Rudolf Wiechert

Routes to New Drugs *

As a chemist engaged in pharmaceutical research, one is often asked about the origin or creation of new drugs. The questioners' own ideas about this question move between two extremes. Some believe that drug research is simply a game of chance, while others are convinced that new substances can now be designed specifically by computer.

I have been actively engaged in drug research for 35 years and, basing on this experience, will now try to explain to you the ways and byways I have taken or seen taken to obtain a new drug. Those involved could relate an interesting story about almost every new drug. Because none of these stories would be the same in all points, it would be futile to try to establish a generally valid scheme which would definitely lead to success. Success does, however, depend on certain preconditions. The most important of these is a group of competent chemists, biologists and physicians who are fully up to date in their respective science. They must be able to recognise something new and to exploit it.

As Louis Pasteur put it so aptly :

"Dans les champs de l'observation,
le hasard ne favorise que les esprits préparés"

The first step towards the development of a new drug is the discovery of a lead substance. A lead substance is a substance with a pharmacological effect which makes the treatment of an illness appear probable. But how does one go about finding such substances *(Figure 1) ?*

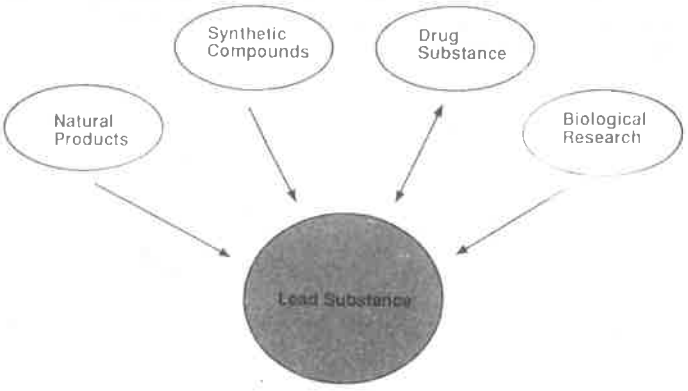


FIGURE 1. - *Sources for lead substances.*

An obvious source is nature. The first drugs came from plants - quinine and opium, for example. The search for natural lead substances still goes on today throughout the entire world - from the bottom of the sea to the depths of the rain forest. Vitally important discoveries were the antibiotic effects of the metabolic products of fungi. Because of the resistance problem, there is still no end to research in this field.

A later method was the isolation of substances from organs. This work led, for example, to the discovery of the sex hormones and many other intercellular regulatory substances. However, it must be remembered here again that the isolation of substances from organs demands basic biological knowledge about the functions and mode of action of the organs.

Molecular biology provided major impulses for the discovery of new biologically active substances. It now helps in the recognition of the molecular basis of certain diseases. In addition, it provides in the form of recombinant proteins the adjuvants required for a specific search for substances - for example the specific points of attack essential for an effect, the receptors.

The development of a chemical industry and the establishment of university institutes for chemistry towards the end of the 19th century soon gave rise to a number of new synthetic products.

These substances are used for what is known as biological random (blind) screening, meaning that the search for lead substances is purely speculative. This procedure is intellectually less satisfactory and appears anachronistic in an age in which everything is designed. However, most of our modern drugs were discovered through this blind screening. One need only mention the antibacterial suphonamides and the psychotropic drugs of the benzodiazepine series to illustrate how vital this method is. Random screening still has a justifiable place in fields where the causes of a particular disease are not yet fully known - tumour and virus diseases, for example.

Substantial research capacity is devoted to improving the active ingredient of a finished drug, the so-called drug substance. The desired improvement can take the form of, for example, better tolerance, a lower dosage or the reduction of a side effect. The method used is to vary the molecular structure systematically by modifications. Surprisingly, this sometimes gives rise to a new lead substance for a field of therapy other than the original.

Last but not least, basic biological research is now increasingly providing clues to new lead substances. A successful way is to investigate the biochemistry of pathological conditions. The study of the pharmacokinetics of an active substance - that is, of its fate in the human body - can also reveal new aspects.

Drug research has the observation and intelligent interpretation of clinical side effects to thank for a number of lead substances. The classical example of this is the development of novel antidiabetics, diuretics, antigout agents, antihypertensives and antiepileptics from the antibacterial sulphonamides.

What I have just said represents a systematisation of ways taken to discover pharmacologically active lead substances. It should be understood primarily only as a didactic division. The reality of substance-finding is so complex that it is necessarily distorted by division.

Research Laboratories of Schering AG Berlin/Bergkamen, D-1000 Berlin 65, Germany.
* *Conférence prononcée, le 4 novembre 1991, lors de la remise du Grand Prix de la Fondation de la Maison de la Chimie au professeur Rudolf Wiechert.*

After these general remarks I should now like to do what I promised to do at the start - explain the ways and byways taken in Schering's laboratories to obtain certain drugs.

The first example is the history of cyproterone acetate *(Figure 2)*. This substance is an antiandrogenic hormone - that is an antagonist of the male sex hormone testosterone. Cyproterone acetate is now the active ingredient of drugs used over most of the earth for the treatment of inoperable carcinoma of the prostate, of acne and signs of virilisation in women, and of hypersexuality in, for example, sex offenders. The effect of the substance was discovered in the 'sixties during a quite different project, namely the search for an orally effective progesterone derivative.

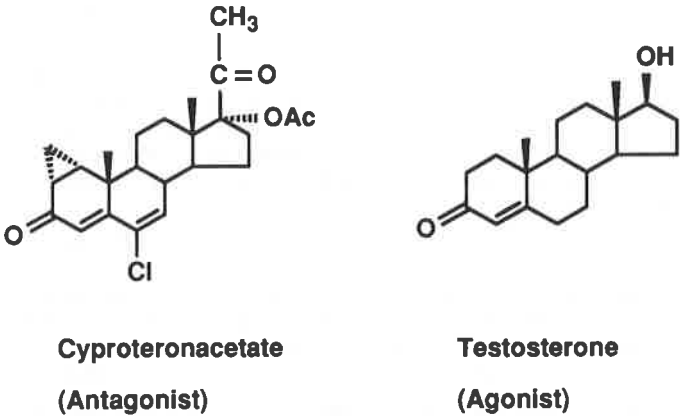


FIGURE 2. - *Cyproterone acetate and testosterone.*

Progesterone *(Figure 3)* is a female sex hormone whose main functions are the preparation and maintenance of pregnancy and regulation of the menstrual cycle. Suitable derivatives of this hormone are best known as constituents of the pill because of their ovulation-inhibiting effect.

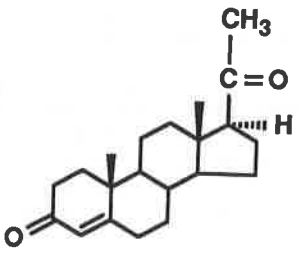


FIGURE 3. - *Progesterone.*

Progesterone has only a weak effect on oral administration. Attempts were therefore made to synthetise an orally more active substance by means of molecular modification.

The ideas about which structural modifications of progesterone might achieve the aim came from the elucidation of the structure of its metabolic products.

In the formulas in the *Figure 4*, the mainly hepatic metabolism and inactivation of the hormone by reductases, hydroxylases and dehydrogenases are presented in simplified form. Reduction of the 20-keto group alone leads to the very weak 20-hydroxy coumpound.

This finding encouraged us to block the fermentative reduction of the 20-keto group by introducing a space-filling substituent in the neighbouring 17-position. One of the many substances synthesised in this way - 17α-acetoxy progesterone - displayed remarkable oral progestational activity and, consequently, was used as the lead substance for a whole class of substances *(Figure 5)*. The structure of 17α-acetoxy progesterone was subsequently modified several times and improved even further in a number of laboratories in the 'fifties and 'sixties.

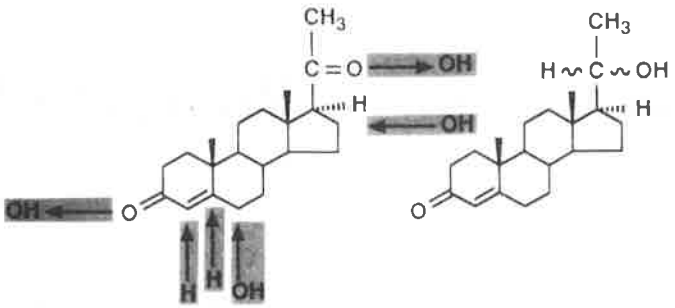


FIGURE 4. - *Biodegradation of progesterone.*

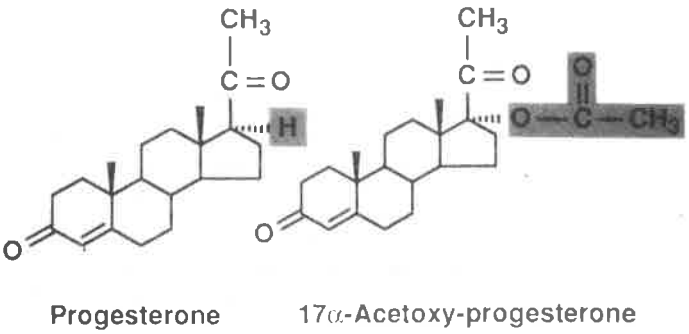


FIGURE 5.

In this same connection, we produced the triene, a substance which can be converted regioselectively and stereoselectively to the 1,2α-methylene compound. We had already observed this surprising type of reaction in another context not specifically, but rather out of playful, experimental curiosity. The introduction of chlorine in 6 position then resulted in cyproterone acetate *(Figure 6)*, which proved to be a highly potent oral progestogen. The compound was chosen as a developmental candidate, and we appeared to have attained our goal.

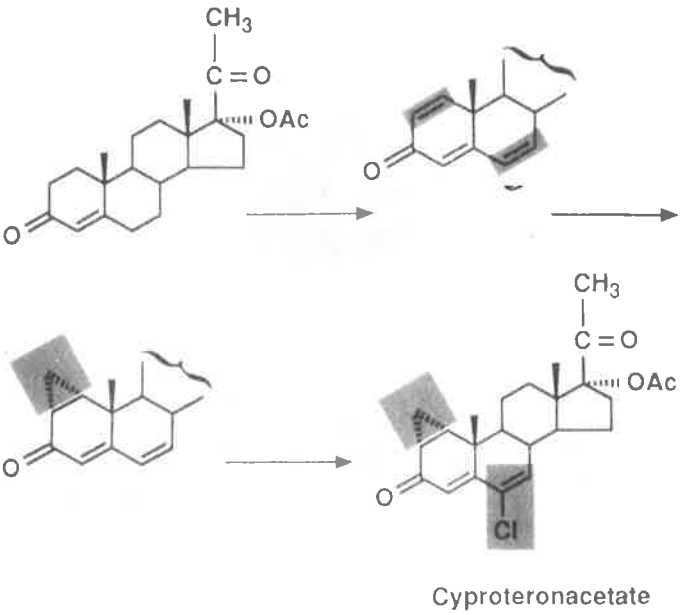


FIGURE 6.

However, we then made an unusual discovery in reproduction-toxicology studies in gestating rats. It is easily possible to differentiate between male and female young by external inspection of the genitals. At first glance, the rats treated with cyproterone acetate had given birth exclusively to female young. Close histological inspection of the foetuses then revealed that all the processes involved in sexual differentiation and which are mediated by androgenic hormones had failed to take place. I should, perhaps, remind you at this point that nothing was known at that time about the molecular mechanism of action of androgenic hormones, a situation which was not made good until Jensen and Jacobson published their basic research work in 1962. The findings in gestating rats meant that cyproterone acetate could no longer be considered for development as a progestogen - and particularly not for contraception. The work of several years therefore appeared to have been in vain. The understandable disappointment of the research team was followed by intensive deliberation on the causes of feminisation. Friedmund Neumann in particular then discovered the antiandrogenic properties of cyproterone acetate by intelligent experiments, elucidated its mechanism of action and pointed out the therapeutic potential.

It then took another 15 years before the drugs for the treatment of prostatic carcinoma and acne developed from cyproterone acetate became a economic success.

Nothing documents the scientific importance of this substance in basic research in the field of hormones better than the several thousand publications which have so far appeared in biochemical and medical journals.

That was the developmental history of cyproterone acetate, which began with a hormone isolated from organs as the first lead substance.

Investigation of the biodegradation of the substance then led to a new lead substance capable of being used as a drug. Purely by chance, yet another lead substance for a different, unplanned use was found while varying the structure to optimise the activity of this more recent lead substance. The developmental pathway illustrates the highly complex procedure involved in substance-finding. Depending on when one lets the story begin, the origin of the lead substances can be placed mentally in one of the 4 boxes *(Figure 1)*.

I now want to report on the developmental pathway of a drug for the treatment of inflammation of the skin. Animals soon die if their adrenals are removed. Adrenalectomised cats injected with extracts of adrenal cortices survive for up to 80 days.

This finding marked the start of a search for substances from the adrenal cortex. A total of 74 substances was isolated by different study groups in Switzerland and the USA between 1935 and 1960.

One of these compounds was cortisone *(Figure 7)* (1936 Reichstein, Kendall, Wintersteiner). No particularly important indications for a clinical application were found in the decade following its discovery. Moreover, the amounts obtained from isolation were not sufficient for larger studies. It was not until 1949 when synthetic cortisone became available that Hench and Kendall of the Mayo clinic reported on their dramatic success in the treatment of rheumatoid arthritis. Numerous laboratories subsequently conducted a succesful search at great expense for more potent synthetic variants of cortisone with fewer side effects. Antiinflammatory corticoids which would have only a topical effect on the skin and no systemic effect were synthetised specifically for inflammations of the skin. In particular, certain esters of highly potent corticoids have come closest to this target.

At that time, fluocortolone (trademark Ultralan) was developed in our laboratories in the form of the 21-caproate or trimethyl acetate *(Figure 8)*. The biodegradation of fluocortolone was studied in man after oral administration. In the course of the studies the α-keto acid was isolated from urine as an unusual degradation product. Although it is ineffective as an antiinflammatory agent, we thought it would be interesting to study the following hypothesis :

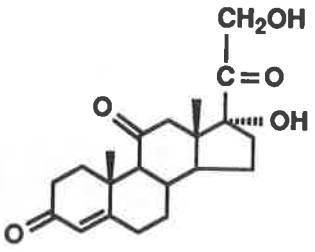
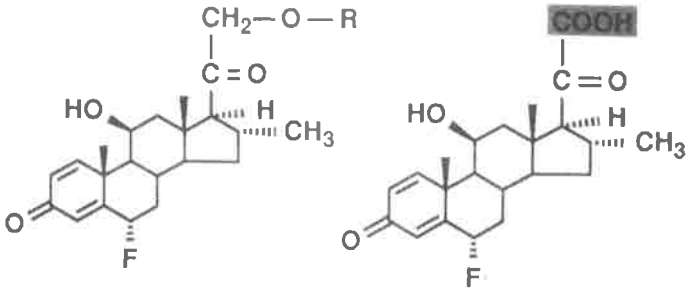


FIGURE 7. - *Cortisone.*



Fluocortolone Metabolite

R = COC_5H_{11}

R = COC_4H_9

FIGURE 8.

It was known from animal experiments and clinical studies that esters act directly *(Figure 9)* on the skin without previous cleavage (partial formula A). It should therefore not be too far fetched to assume that the so similar, so to speak reversed esters of the degradation product (partial formula B) would be active. They would have the major advantage that, after cleavage in the body, they would certainly not be systemically active, since the acid is inactive.

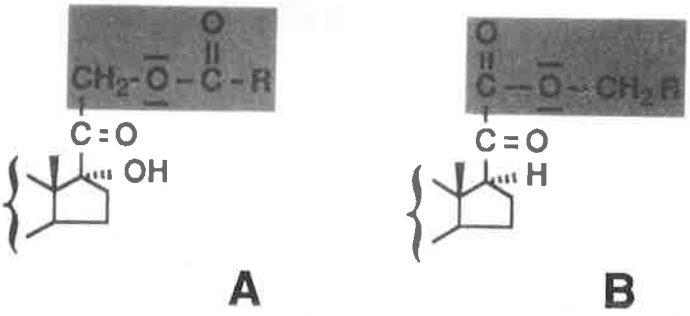


FIGURE 9.

Carbonic acid butyl ester (Vaspit®, *Figure 10)* did, in fact, fulfil all the hopes placed in it. The compound is important under the trademark Vaspit for the treatment of inflammations of the skin particularly in infants and pregnant women. In this case, the impulse for its synthesis came from the pharmacokinetics. However, a major contribution - namely the knowledge that esters as such do work - came from clinical studies.

One could come to a false conclusion from the results of the 2 projects described, both of which started from natural substances. The following impression might be created : Once a bio-

logically active natural substance has been identified, then some success in the development of a drug is certain. This is not, however, the case, as the next example will show.

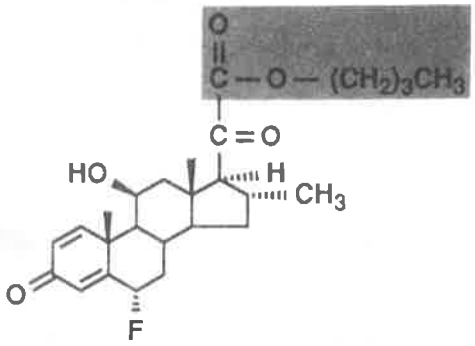


FIGURE 10. - *Vaspit.*

Insect development proceeds from laval stages via a pupal stage to the insect *(Figure 11)*. In 1954, Butenandt and Karlson isolated the substance which causes these ecdyses, or skin shedding, and called it ecdyson. At that time, they extracted 25 mg ecdyson from half a ton of silk moth pupae.

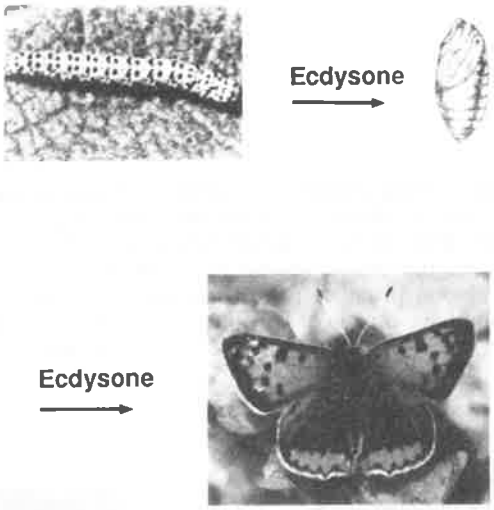


FIGURE 11.

An interesting observation which was to be of major general biological importance was made during experiments to elucidate the mechanism of action : It was demonstrated that ecdyson has a direct effect on genetic material - the experiments seem to indicate activation of the synthesis of ribonucleinic acid. This led to the hypothesis of a possible influence on protein synthesis. It was not until nine years later that the structure of ecdyson was elucidated. It was found to be a complicated sterol derivative.

After the structure had become known, we began to synthetise ecdyson in collaboration with a group from Hoffmann La Roche and Co. AG in Basle under Andor Fürst. The result was that we were able to produce the hormone from ergosterol in 14 highly complicated steps *(Figure 12)*. We synthetised about 100 g ecdyson from 1 000 kg ergosterol and made it available for pharmacological studies in warm-blooded animals. The result was a great disappointment - we did not find any effects at all. Researchers at Böhringer Mannheim GmbH reported in detail on another unsuccessful project, the lead substance of which was an endogenous, pharmacologically active substance. They were trying to develop agents for, for example, the treatment of angina pectoris by varying the molecule of the vasodilatory substance adenosin. In fifteen years, a total of 2 000 compounds was synthetised and 36 patents applied for. The research costs amounted to about 100 million DM. The project was finally abandoned during the clinical investigation in patients because of intolerable side effects.

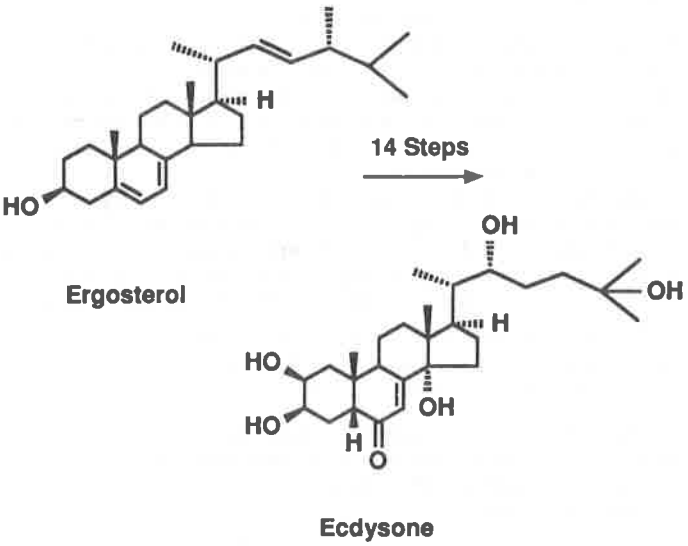


FIGURE 12. - *Production of ecdyson from ergosterol in 14 steps.*

As mentioned at the start, basic research into the clarification of the biochemical causes of diseases is a very promising way of discovering new lead substances. A large number of laboratories is working particularly intensively and successfully on the synthesis of enzyme inhibitors, which work as follows *(Figure 13)* :

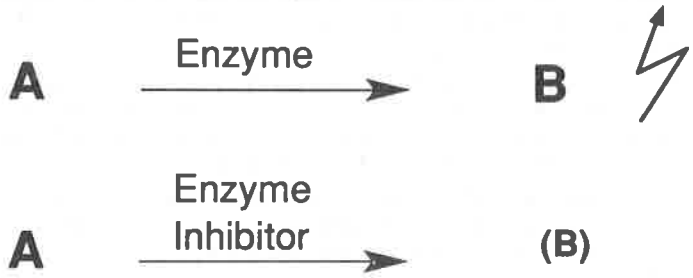


FIGURE 13.

An endogenous substance A is converted to the pathogenetic substance B by a specific enzyme. The formation of B is prevented or reduced by blocking the enzyme with an inhibitor. A knowledge of this process in the body with the components A, B, the enzyme and the typical symptoms of the disease is therefore a precondition for the discovery of an inhibitor. If this precondition is met, the chemist can design and synthetise appropriate inhibitors with a good chance of success. This is because the substance A is usually structurally similar to the inhibitor.

Over the last few years, both we and several other research groups have been working on the development of inhibitors of oestrone biosynthesis. The therapeutic potential of such compounds lies in the treatment of oestrogen-dependent mammary tumours and of benign prostatic hyperplasia, a common complaint in advanced age.

In the body, oestrone arises from androstenedione at the end of a long chain of synthesis mediated by the enzyme aromatase *(Figure 14)*. To find an aromatase inhibitor, we and others therefore synthetised a large number of variations of androstenedione.

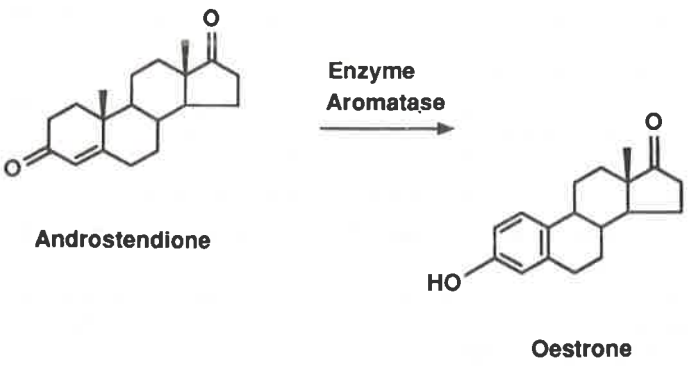


FIGURE 14. - *Synthesis of oestrone.*

At Schering, we chose the 1-methyl compound, "Atamestan" *(Figure 15)*, for clinical testing after extensive pharmacological studies. The aromatase is only one constituent of a multi-enzyme complex, so the choice of "Atamestan" was more complicated than suggested here.

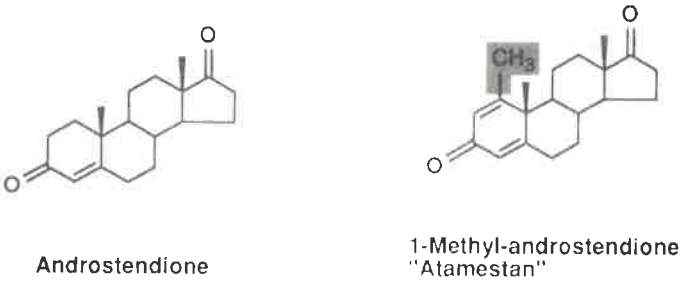


FIGURE 15. - *Synthesis of Atamestan.*

I should like to end my report with a brief and simplified overview of some uses of computer technology in the search for lead substances.

It has already been mentioned that the first step towards the biological effect of a substance is its binding to a specific endogenous receptor. Receptors are high-molecular proteins.

The chances of finding lead structures are good if the exact spatial structures of the receptor and substance are known. Computer graphics and programmes can then be used to determine the structure (that is, the geometry and charge distribution) of the so-called receptor-substance complex *(Figure 16)*.

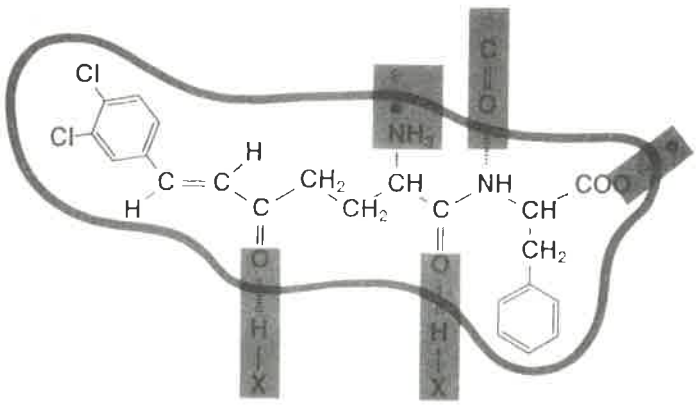


FIGURE 16. - *Substrate-receptor-complex.*

This gives us an insight into the positions at which and the binding forces by which receptor and substance are held together.

The diagram in this figure shows us examples of these bonds - a hydrophobic pouch at the top left, hydrogen bridge bonds and cation-anion interactions.

The result of such studies is, therefore, a knowledge of the essential structural parts of the active substance - of the so-called pharmacophor - which are required for binding to the receptor and, therefore, for the induction of an effect.

In this ideal case, the chemist obtains the rational basis for a drug design.

The possibilities for new structures arising from this can go beyond the imagination of the scientist. When this happens, resort is made to data banks of structures.

Even if the 3-dimensional structure of the receptor is unknown - which is the normal case in practice -, computer technology can provide valuable assistance.

By means of comparative analysis of a large number of active and inactive compounds, it can provide a hypothetical model of the essential parts of the substance. A likeness of the receptor can be modelled on the basis of such a pharmacophor model. The name given to this procedure is receptor mapping.

We employed this method in a project to find novel anxiolytic substances. A description of the many-sided biological goal of this project would be too involved here *(Figure 17)*.

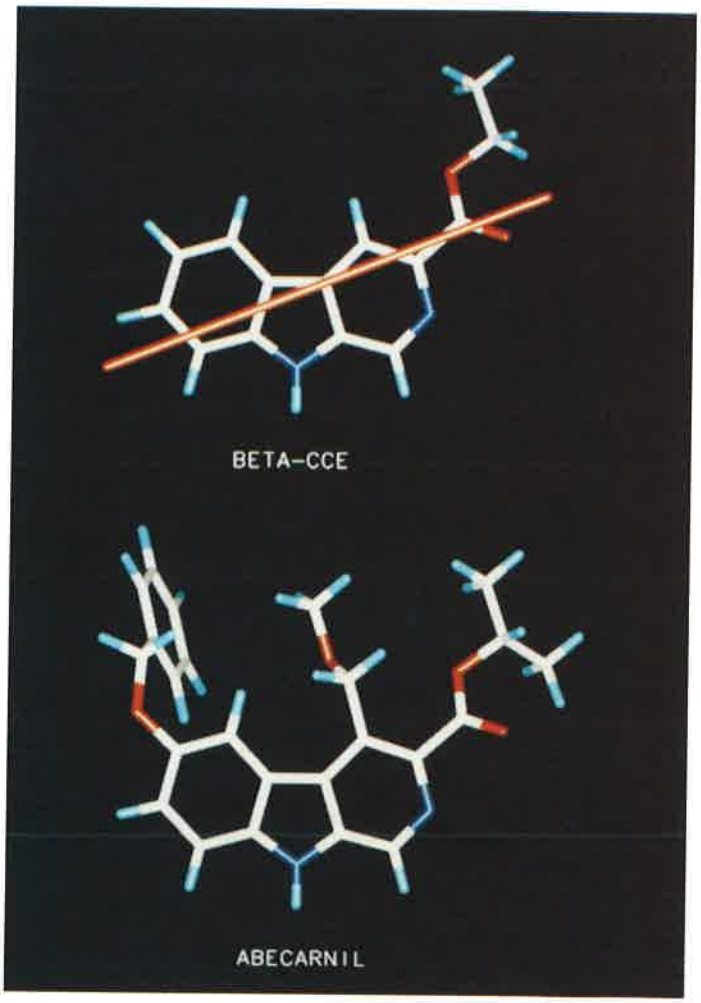


FIGURE 17. - *Synthesis of Abecarnil.*

The starting point was the ß-carboline-3-carbonic acid ethylester (ß-CCE). The ester was isolated from urine in Denmark (Braestrup) in 1980. It displays marked affinity for the benzodiazepine receptor. The group of benzodiazepines includes, for example,

the well-known psychotropic drug Valium. Together with a Danish study group, we have synthesised more than 3 000 ß-carbolines. One compound, "Abecarnil" is now in an advanced stage of clinical development.

As a result of computer assisted studies in this series, we are able to draw certain conclusions about the binding to the receptor :

The primary anchoring of the active substances takes place via the region lying below the red line ; it contains the two nitrogen atoms and carbonyl oxygen.

The quality of the action is regulated by appropriate substitution in the area lying above the red line.

The methoxymethyl group is probably an auxilliary binding site. The ester function is replaceable. The phenyl ring on the first ring must probably stand perpendicular to the basic structure.

These conclusions alone give rise to a number of hypotheses for possible receptor-substance complexes and provide the impulse for the synthesis of a great number of potentially active structures.

This brings me to the end of my short excursion on routes to new drugs. My aim was to give you a comprehensible insight into the practice of searching for new substances.

The first decisive step in drug research - the discovery of a lead substance - should be given more and more a rationally direct rather than an incidental or empirical basis.

I believe that there are justifiable reasons for this hope.

Knowledge of the communications and regulatory systems of the human body is growing very quickly.

The basis for patho-biochemically orientated research and knowledge about the molecular principles of how effects are induced are also growing rapidly.

This knowledge can now be put into practice by means of modern methods of information technology and last, but not least, the repertoire of organosynthetic chemistry is also growing continuously.

Because of the complicated structure of the biological system "man", however, drug research can never become exact mathematical science.