Drug Design—Possibilities and Limitations*

By E. J. ARIËNS
Department of Pharmacology, University of Nijmegen (The Netherlands)

Drug design is the effort to develop bioactive compounds (pharmaca including pesticides, food additives, cosmetics as well as therapeutics) on as rational as possible a basis, which implies a reduction of the trial-and-error factor to the possible minimum. Generally a chemical compound with a particular biological action constitutes the starting-point—the lead—for a purposeful modulation of the action by appropriate chemical modification (1, 2, 3, 4, 5, 12, 13, 22). This procedure preassumes a structure-action relationship and some understanding thereof.

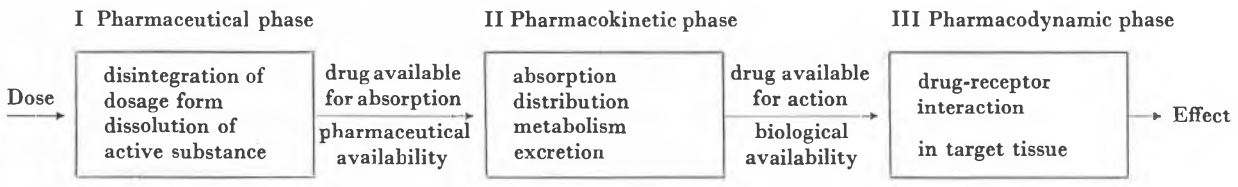
In drug action three main phases are to be distinguished. The pharmaceutical phase, determinant for the concentration of the drug available for absorption. In the case of pesticides, food additives, etc. the term application phase might be used. Then follows the pharmacokinetic phase comprising absorption, distribution, excretion and metabolic conversion of the drug, determinant for the concentration of the active compound in the target tissues and at the sites of action—the specific receptors. Finally the pharmacodynamic phase, in which the interaction between the drug and the sites of action and therewith the induction of a stimulus and thus the generation of the effect takes place. The processes in the various phases are of a chemical and physicochemical nature. Thus the action and activity of a drug observed with a particular type of biological object is determined by the complex of chemical properties —the structure—of the compound concerned. Structure-action relationship, therefore, is a fundamental characteristic for bioactive compounds. The apparent lack of such a relationship can only be due to a deficiency of the methods of investigation and the mutiplicity and complexity of the processes involved. Structure-action relationship as a rule is more clear in the less complex *in vitro* studies. In the efforts to detect structure-action relationships and to adjust the chemical structure to particular requirements in drug design, emphasis is put on the significance of particular chemical groups (moieties) in the pharmacon for particular aspects of its action (1, 2, 3, 4, 5).

The three main phases that can be distinguished in drug action (Scheme 1) also are reflected in Drug Design. The main aspects thereof are: The search for new leads—compounds with a particular bioactivity—and the elimination of unwanted components in the action, which covers the pharmacodynamic phase. The adaptation of the properties of the compound selected to special requirements for distribution and time-concentration relationships, which covers the pharmacodynamic phase. The optimal formulation of the drug thus obtained for practical application, which covers the pharmaceutical phase.

New leads are obtained by: identification of biologically active natural products, screening of chemicals, in general, and especially of compounds with new unprecedented structures for biological action, analysis of the effects, including evaluation of the side-effects of drugs as potentially useful actions, testing of drug metabolites for a possible activity, and the study of biochemistry and pathochemistry or, in general, the fundamental processes of life. Bioactive compounds derived from biochemical leads are, for instance, the metabolic inhibitors: enzyme inhibitors and antimetabolites or antivitamins. Usually these are chemically clearly related to the corresponding metabolites or vitamins. Especially substitutions close to the moiety involved in the conversion or action of such molecules lead to inhibitors. α-Alkyl substitution in esters, amines, amino acids, etc. often results in compounds being resistant to and acting as inhibitors of the enzymes concerned. A special class are the "active-site-directed" irreversibly blocking agents. These are substrate molecules in which in a suitable position alkylating or acylating moieties are introduced, able to form covalent bonds with groups in the neighbourhood of the active site on the enzyme (exoalkylation). A large variety of reversible and irreversible metabolic inhibitors are reported in the literature (7, 8, 15, 16, 20, 21, 23, 24, 25). Only very few of them, how-

* Abstract of a lecture given at the Spring Meeting of the Swiss Chemical Society in Zurich, April 21/22, 1972.

Scheme 1



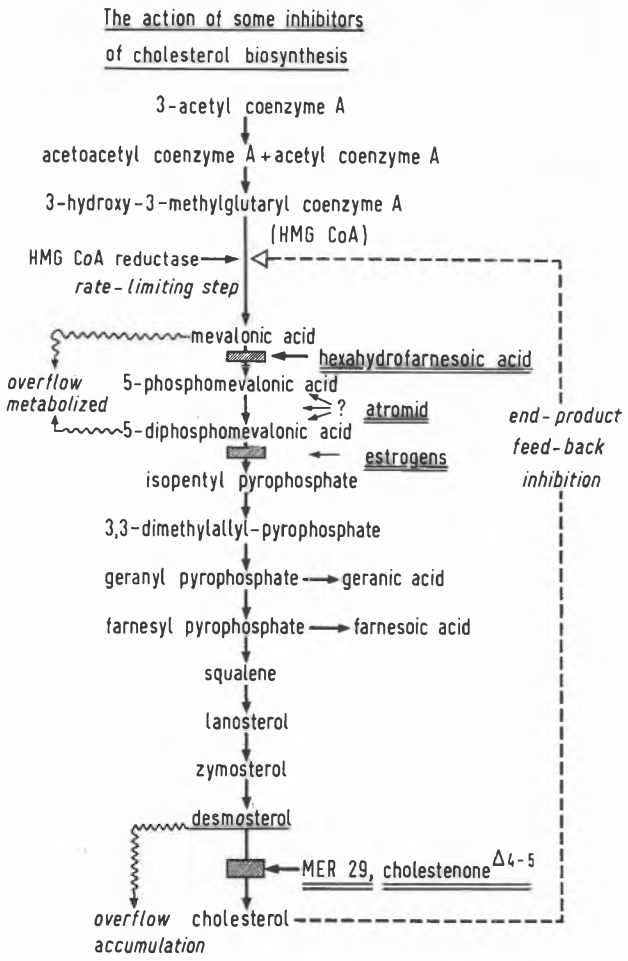


Figure 1

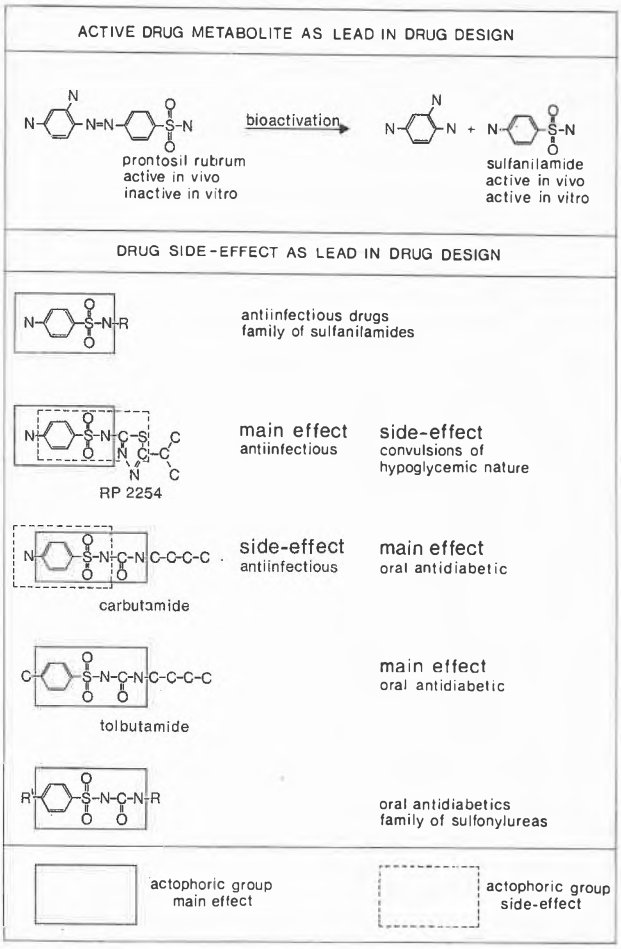


Figure 2

ever, are of practical use. Examples are the folic acid reductase inhibitors, the purine and pyrimidine analogues, used as cytostatics in cancer therapy and known for their high toxicity, and the organic phosphates used as insecticides, but also highly toxic to mammals. The lack of selectivity in action of the metabolic inhibitors is inherent in their mechanism of action and in the universality of the biochemical principles throughout nature. Selectivity in action requires species differences in biochemistry. For the antivitamins not only their lack of species selectivity but also the fact that vitamins often serve as a co-factor for a variety of enzymes is a serious drawback. The selectivity in action of certain useful antiinfectious agents such as the sulfanilamides (para-aminobenzoic acid antagonists) and the penicillins is based on such species differences. *p*-Aminobenzoic acid serves as a precursor for the folic acid synthesis in micro-organisms while higher animals use folic acid itself as a vitamin. Penicillin interferes with the synthesis of cell walls, which are required by micro-organisms, but are not existent in higher animals.

The enzymes of various species, although isodynamic (which means that they perform identical reactions) may slightly differ in the structures surrounding the active site (iso-enzymes). Hitchings, using folic acid reductase of bacterial and mammalian origin, succeeded in developing inhibitors with selectivity in action on basis of such differences (13, 14). In this regard also the irreversible "exo-alkylating" enzyme inhibitors offer certain promises. Comparative biochemistry will point the way to selectivity in action. Even if no species selectivity is required, metabolic inhibitors may nevertheless fail. This can be elucidated by, e.g., the antimetabolite Δ 4–5 cholestenone, designed to inhibit cholesterol synthesis. It blocks the conversion of desmosterol to cholesterol (fig. 1) and thus rules out the feed-back control which is normally performed by cholesterol. The consequence is an unrestricted formation of the intermediate desmosterol, which tends to overrule the blocking agent and to accumulate in the tissues. Compounds designed to regulate metabolic processes should act preferentially on the enzyme which constitutes the natural site for regulation. This as a rule is the first step after branching in a biochemical pathway, which often concerns the rate-limiting enzyme. Compounds acting as blockers of the site for substrate conversion as well as mimetics or antagonists for the feed-back regulators, acting on the allosteric sites might allow efficient interference with the

biochemical pathways concerned (6, 10, 11, 17). Insight in the regulatory processes on the level of enzyme synthesis, enzyme function, etc. may point the way to the design of new appropriate artificial metabolic regulators.

An active drug metabolite that served as a lead for the development of new drugs is the metabolite of prontosil rubrum: sulfanilamide; it can be considered as the mother compound for a wide variety of antiinfectious sulfanilamides (fig. 2). Various examples of the application of drug metabolites as drugs or as leads for drug design are reported in literature (1, 5).

Development of a side-effect to a main action is a common procedure in drug design. Certain antiinfectious sulfanilamides show a convulsive action as a side-effect, which was classified by LOUBATIÈRES, as hypoglycemic in nature (15a). This action was recognized as potentially useful in diabetes. From this lead, *via* antidiabetics with the original antiinfectious action as a side-effect (carbutamide) pure oral antidiabetics (tolbutamide) and subsequently a range of related compounds (short- and long-acting, weakly and highly potent) were developed (fig. 2). Various now highly appreciated drugs originate from the cultivation of originally "unwanted" side-effects (1, 5).

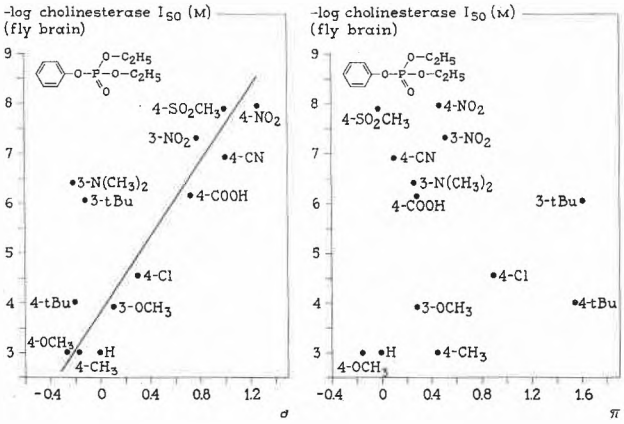


Fig. 3. The relationship between (a) σ (HAMMETT constant), and (b) π (according to HANSCH) for the action of a series of ring-substituted phenylphosphate esters on fly brain cholinesterase expressed as molar 50% inhibitory values. Note that only plotting against σ which is an indicator for the reactivity in the phenolic OH group and therewith for the stability of the ester link results in a clear-cut correlation. The lipid solubility represented by π and therewith indifferent hydrophobic binding apparently has no predominant influence. Since the action on the enzyme is involved, no lipid membranes have to be passed which implies that also in this respect no dependency on π is expected. (a) after FUKUTO and METCALF, *Agr. Food Chem. 4* [1956] 930, (b) after HANSCH and FUJITA, *J. Amer. Chem. Soc. 86* [1964] 1620

Once a suitable pharmacodynamic principle has been established and chemically identified, optimalization must follow. This implies elimination of unwanted side-effects followed by adaptation with regard to the pharmacokinetic and pharmaceutical requirements. Optimalization thus clearly is a multifactorial problem. Important chemical parameters are the partition coefficients, which mainly govern distribution by diffusion, and the sterical location, size and charge distribution of the various moieties in the drug molecule which govern metabolic degradation, active transport, indifferent binding to tissue components, and especially drug-receptor interaction. Modulation of the chemical properties and therewith of the biological action always implies modification of particular moieties of the drug molecule, thus leading to derivatives of the mother compound. Insight in structure-activity relationship, therefore, is based on a moiety approach. Correlations between biological activity and the HAMMETT substituent constants (σ, related to charge distribution) and the HANSCH substituent constants (π, related to partition coefficients) are extensively studied. Such studies may supply useful information with regard to promising chemical groups or substituents, especially if particular aspects, such as enzyme inhibition (fig. 3), skin penetration, etc. are considered. The relations will be less clear in case of mutifactorial *in vivo* studies.

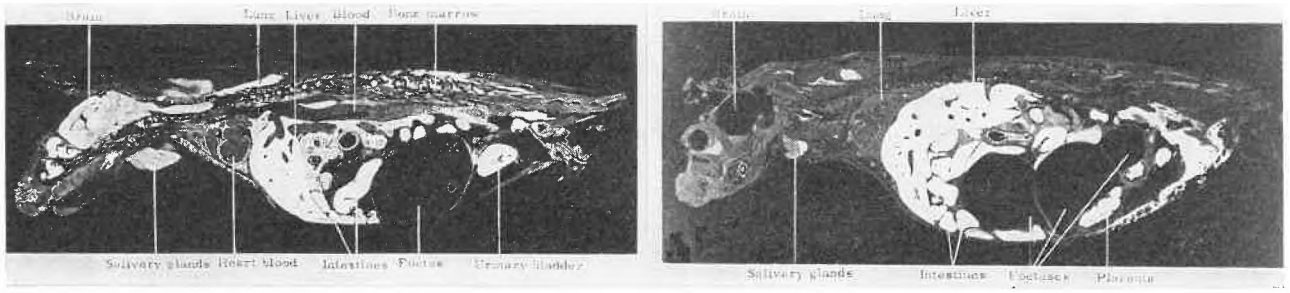
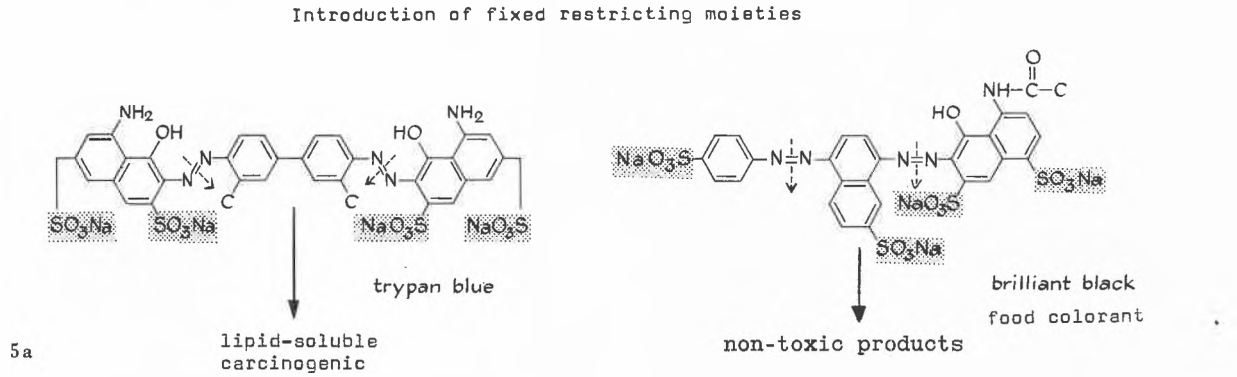


Fig. 4. A comparison of the distribution and excretion of two antihistamines, the tertiary promethazine and the quaternary (Aprobit) phenothiazine compound labeled with ^{35}S. Note the high concentrations of the tertiary amine in brain tissue and the restriction in the distribution of the quaternary compound mainly to the liver and the intenstines (after HANSSON and SCHMITERLÖW, *Arch. Int. Pharmacodyn. 131* [1961] 309)

From the biological point of view, too, certain moieties in the drug molecule may play a particular role. Strongly polar, e.g., highly ionized groups in a drug molecule will limit penetration of lipid barriers and thus restrict distribution mainly to the extracellular fluid compartments. They also exclude actions on the central nervous system, since the lipophilic blood-brain barrier cannot be passed by such compounds (fig. 4). The restriction in the distribution, together with a rapid urinary excretion of these hydrophilic compounds, will reduce toxicity. Quaternized antihistaminics and anticholinergics are devoid of central nervous system actions. Azo dyes bearing highly ionized sulfonic acid groups in the various moieties linked by the azo groups are acceptable as food colorants because of their low toxicity (fig. 5a). The restricting moieties mentioned may be an intrinsic part of the drug molecule in its active form like in the case of the quaternized antihistaminics. They also may be disposed of before action, like is the case with the ionized succinyl and phthalyl groups (disposable restricting moieties) in the enteric sulfanilamides which are restricted in their intestinal absorption and gradually release the active free sulfanilamide in the intestinal lumen (fig. 5b). Moieties which shift the solubility of a compound to the lipophilic side will, unless this is overdone, facilitate absorption and tissue penetration. Introduction of hydrocarbon groups as fixed or disposable facilitating moieties is widely applied (see fig. 5c and d). Compounds selectively accumulated by active transport processes in particular tissues are used as moieties which regulate the distribution in a selective way. The radiopaque for cholecystography tetragnost, an iodinated derivative of phenolphthalein, is, like the latter compound itself, actively accumulated in the bile. Phenolphthalein serves as a fixed selecting moiety conducting the radiopaque iodine atoms in the molecule to the compartment required (fig. 5e) (1, 4, 5).

Moieties in a drug molecule which are sensitive to attack by enzymes, such as ester groups, can be indicated as vulnerable moieties. Introduction of such moieties into a compound may imply a rapid bioinactivation and thus a short action. Ultra-short acting compounds are obtained by introduction of vulnerable moieties, and long acting compounds by stabilization or elimination of such moieties (fig. 5f and g). Under circumstances enzymatic conversion may imply bioactivation of a precursor compound. If the enzymes involved in the biochemical conversion prevail outside or inside the target tissue or target species, introduction of suitable vulnerable moieties can lead to compounds which are selectively bioinactivated outside (fig. 5h) or selectively bioactivated inside the target (1, 4, 5).

Time-concentration relationship and therefore time-response relationship can be modulated by the formation of e.g. poorly water-soluble compounds. Esters of steroids and fatty acids used as depot preparations are examples. The fatty acids serve as disposable desolubilizing moieties (fig. 5i). In an analogous way water-soluble compounds can be obtained by hemi-esterification with dicarbonic acids, e.g. succinic acid, which then serve as



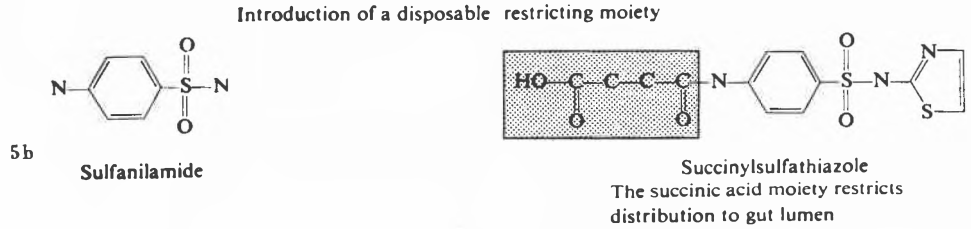
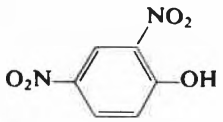


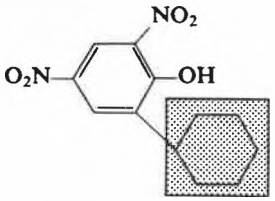
Figure 5

Introduction of a fixed facilitating moiety

5c



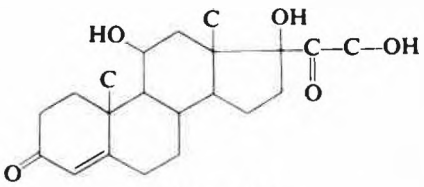
Dinitrophenol
Insecticide



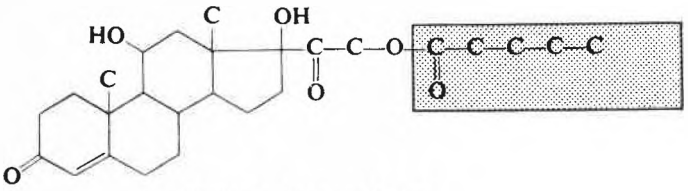
Dinex
Penetrates more easily in the targets because of its high lipophility

Introduction of a disposable facilitating moiety

5d



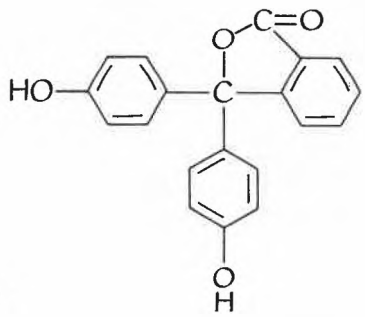
Hydrocortisone
Glucocorticoid



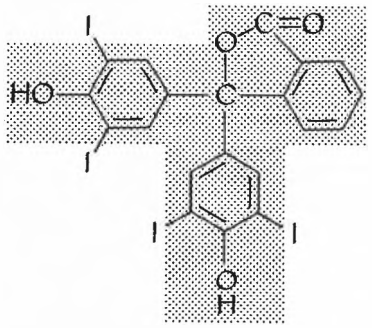
Hydrocortisone valeriate
Penetrates more easily into the skin because of its higher lipophility

Use of phenolphthalein as a fixed selecting moiety

5e



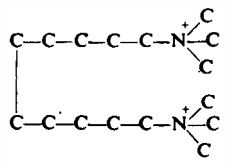
phenolphthalein
(excreted in bile)



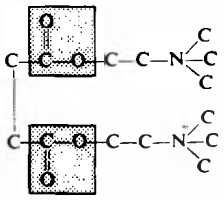
tetraiodophenolphthalein
(biliary radiopaque)

Introduction of a vulnerable moiety

5f



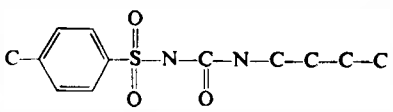
Decamethonium
Muscle relaxant



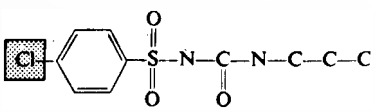
Succinylcholine
Sensitive to plasma esterase
Short-acting muscle relaxant

Elimination of a vulnerable moiety

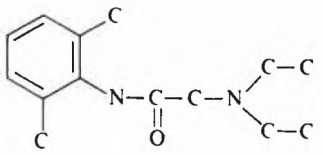
5g



Tolbutamide
Rapidly oxidized to inactive carboxyl derivative
Short-acting ($t_{\frac{1}{2}}$ = 5–7 hr)

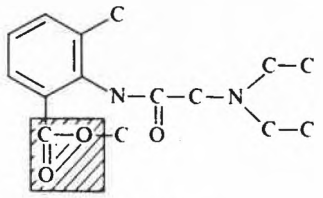


Chlorpropamide
Metabolically stable
Long-acting ($t_{\frac{1}{2}}$ = 33 hr)

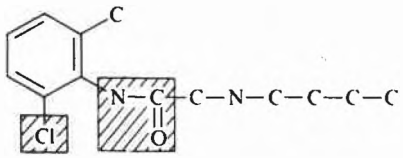


Lidocaine
stable local anesthetic

5h



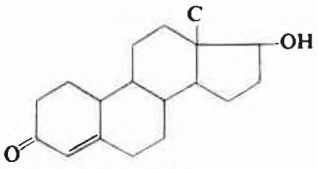
Tolycaine
introduction of the vulnerable moiety implies rapid bioinactivation once general circulation is reached



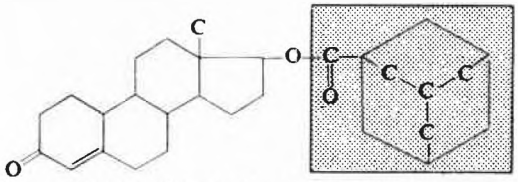
Butanilicaine
destabilization of the acylamide group implies rapid bioinactivation once general circulation is reached

Introduction of a disposable desolubilizing moiety

5i



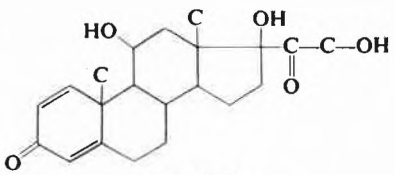
Nortestosterone
Anabolic steroid



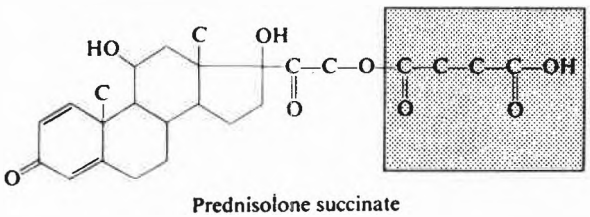
Nortestosterone adamantane carboxylate
Extremely lipophilic derivative
Depot preparation

Introduction of a disposable solubilizing moiety

5j



Prednisolone
Glucocorticoid



Prednisolone succinate
The disposable moiety confers water solubility to the steroid

disposable solubilizing moieties. Such hemi-esters are suitable for intravenous injection and are used to obtain rapidly high concentrations of the active product in the plasma (fig. 5j). The rate of hydrolysis of the ester is a determinant factor, here too.

The idea of the molulation of distribution of bioactive compounds by introduction of particular moieties is also applied in the design of insecticides, fungicides and weed killers and is of special importance for pollution control (1, 4, 5).

Modulation of bioactivity by application of the principles outlined and optimalization on basis of the more sophisticated physicochemical approach are the basis for drug design. This, no doubt, is a multidisciplinary enterprise.

References

1. Ariëns E.J., *Progress in Drug Research 10* (1966) 431 (Editor: E. Jucker), Birkhäuser, Basel.
2. – *Ann. Ist. Super. Sanità 3* (1967) 412.
3. – *Il Farmaco* (Ed. Sc.) *23* (1968) 52.
4. – *Pure & Appl. Chem. 19* (1969) 187.
5. *Drug Design*, vol. I and II, Academic Press, New York 1972.
6. Atkinson D.E., *Science 150* (1965) 851.

7. BAKER B.R., *Design of Active-Site-Directed Irreversible Enzyme Inhibitors*, Wiley, New York 1967.
8. BÜCHER TH. and H. SIES, *Inhibitors Tools in Cell Research*, Springer, Berlin 1969.
9. BURSTEIN C., M. COHN, A. KEPES and J. MONOD, *Biochim. Biophys. Acta 95* (1965) 634.
10. CHANGEUX J. P., Subunit Structure of Proteins, *Brookhaven Symposia in Biology 17* (1964) 233.
11. GREEN D.E. and R.F. GOLDBERGER, *Molecular Insights into the Living Process*, p. 30, 90, 306, Academic Press, New York 1967.
12. HARPER N. J., *Absorption and Distribution of Drugs*, p. 103 (Editor: T.B. BINNS), E. and S. Livingstone Ltd., Edinburgh 1964.
13. HITCHINGS G. H., *Chemotherapy of Cancer* (Editor: P. A. PLATTNER), p. 77, Elsevier, Amsterdam 1964.
14. – and J.J. BURCHALL, *Advances in Enzymology 27* (1965) 417 (Editor: F.F. NORD), Wiley, New York.
15. HOCHSTER R.M. and J.H. QUASTEL, *Metabolic Inhibitors*, vol. I and II, Academic Press, New York 1963.
15a. LOUBATIÈRES A., in *Oral Hypoglycaemic Agents* (Editor: G.D. CAMPBELL), p. 1, Academic Press, New York 1969.
16. MARTIN G.J., *Biological Antagonism*, Blakiston, Philadelphia (Pa.) 1951.
17. MONOD J., *Endocrinol. 78* (1966) 412.
18. – G. COHEN-BAZIRE and M. COHN, *Biochim. Biophys. Acta 7* (1951) 585.
19. MÜLLER-HILL B., H.V. RICKENBERG and K. WALLENFELS, *J. Mol. Biol. 10* (1964) 303.
20. PETERS R.A., *Biochemical Lesions and Lethal Synthesis*, Pergamon Press, London 1963.
21. RHOADS C.P., *Antimetabolites and Cancer*, Bailey Bros. & Swinfen Ltd., London 1955.
22. TISHLER M., Molecular Modification in Modern Drug Research, *Advances in Chem. Series 45* (1964) 1 (Editor: R.F. GOULD).
23. WEBB J.L., *Enzyme and Metabolic Inhibitors*, vol. I., 1963, vol. II and III, 1966, Academic Press, New York.
24. WOLSTENHOLME G.E.W. and C.M. O'CONNOR, *Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity*, J. & A. Churchill Ltd., London 1958.
25. WOOLLEY D.W., *A Study of Antimetabolites*, Wiley, New York 1952.