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STEREOSELECTIVITY OF BIOACTIVE XENOBIOTICS

A PRE-PASTEUR ATTITUDE IN MEDICINAL CHEMISTRY, PHARMACOKINETICS AND CLINICAL PHARMACOLOGY

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STEREOSELECTIVITY, A NATURAL ASPECT OF MOLECULAR BIOLOGY

Life processes are characterised by a high level of dynamic organisation requiring an intricate regulatory network for inter- and intracellular communication and for communication between living systems and their environment. Conveyance of information is largely controlled by "messenger" molecules which selectively interact with particular sites on enzymes, receptors, carrier molecules, etc., essential components constituting to the basis of life. Drugs and pesticides, like pheromones, can be regarded as exogenous messengers. They too are designed for particular functions and are "released" under particular conditions. Like endogenous messengers, they as a rule act on specific sites on receptors, enzymes, etc. Endogenous as well as exogenous messengers can be subject to activation and/or inactivation by metabolic conversion. Examples are (pre)hormones, (pro)drugs and (pro)pesticides.

Nature, fauna and flora, at first sight shows a high degree of symmetry, but on the molecular level asymmetry dominates. The selectivity, the discriminatory capacity of the specific sites for messenger molecules and substrates, is based upon complementary chemistry. This can be visualised as a key and lock principle, not as something static but as a dynamic process of mutual adaptation, an "embracement" between substrate and enzyme, or messenger molecule and receptor. The complementary principle concerns the charge distribution at the interface of the interacting molecules and the spatial structure of the interactants. Stereoselectivity of biological systems and stereospecificity in the action of chiral bioactive xenobiotics is a "natural" matter. The concept of stereochemistry and stereoselectivity in biological processes goes back to Pasteur and van't Hoff–Le Bel, about a hundred years ago. In their memoirs [1] Pasteur stated: "Most natural organic products, the essential products of life are asymmetric and possess such asymmetry that they are not superposable on their images. . . . This establishes perhaps the only well marked line of demarkation that can at present be drawn between the chemistry of dead matter and the chemistry of living matter."

Chirality, stereoselectivity and stereospecific production of chemicals are characteristics of nature. Many of the xenobiotics obtained by organic syntheses are chiral too. Contrary to the natural products, synthetics are usually obtained as isomeric mixtures such as racemates. This situation may rapidly change with the development of stereospecific catalytic methods, including biomimetic methods, which rely on the help of enzymes as catalysts. Stereospecific syntheses and/or separation of stereoisomers were, and to a certain extent still are, laborious tasks. As a consequence, most of the synthetic chiral agents applied as drugs, pesticides, etc. are marketed as racemic mixtures or, in general, as mixtures of isomers (Fig. 1a, b, c). These figures illustrate that the line of demarkation between chemistry of dead and living matter postulated by Pasteur still holds largely true for producers of drugs and pesticides.

MEDICINAL CHEMISTRY, A SOPHISTICATED DISCIPLINE

The development of new, highly active and selective bioactive agents, particularly drugs and pesticides, has evolved over the past years to a skill integrating organic chemistry, physical chemistry and biochemistry, closely intertwined with biology in its widest sense. The advancement in the concepts and techniques involved is remarkable. An example is the study of Quantitative Structure–Activity Relationships (QSAR) by means of the Hansch approach, based upon physico-chemical structural descriptors such as π, σ and E_S, extended with the sterimol parameters [2]. Another example is the information gathered from structural X-ray analysis and quantum mechanical approaches. The exploitation of the insight thus gained in computer-directed organic synthesis, embedded in personal experience, has given the medicinal chemist leads to develop highly potent, sometimes even extremely potent agents. In the biological evaluation, multivariate data analysis, pattern recognition programs, receptor-mapping, pharmacophore identification, and computer-assisted curve-fitting (particularly in pharmacokinetic studies) have proved to be most helpful [3].

A highlight are the interactive computer-graphic techniques with which molecules are presented in a three-dimensional shape with coloured surfaces for polar, highly polar and hydrophobic areas. Every medicinal chemist and biologist involved in the study of drugs or pesticides will have enjoyed the beautiful

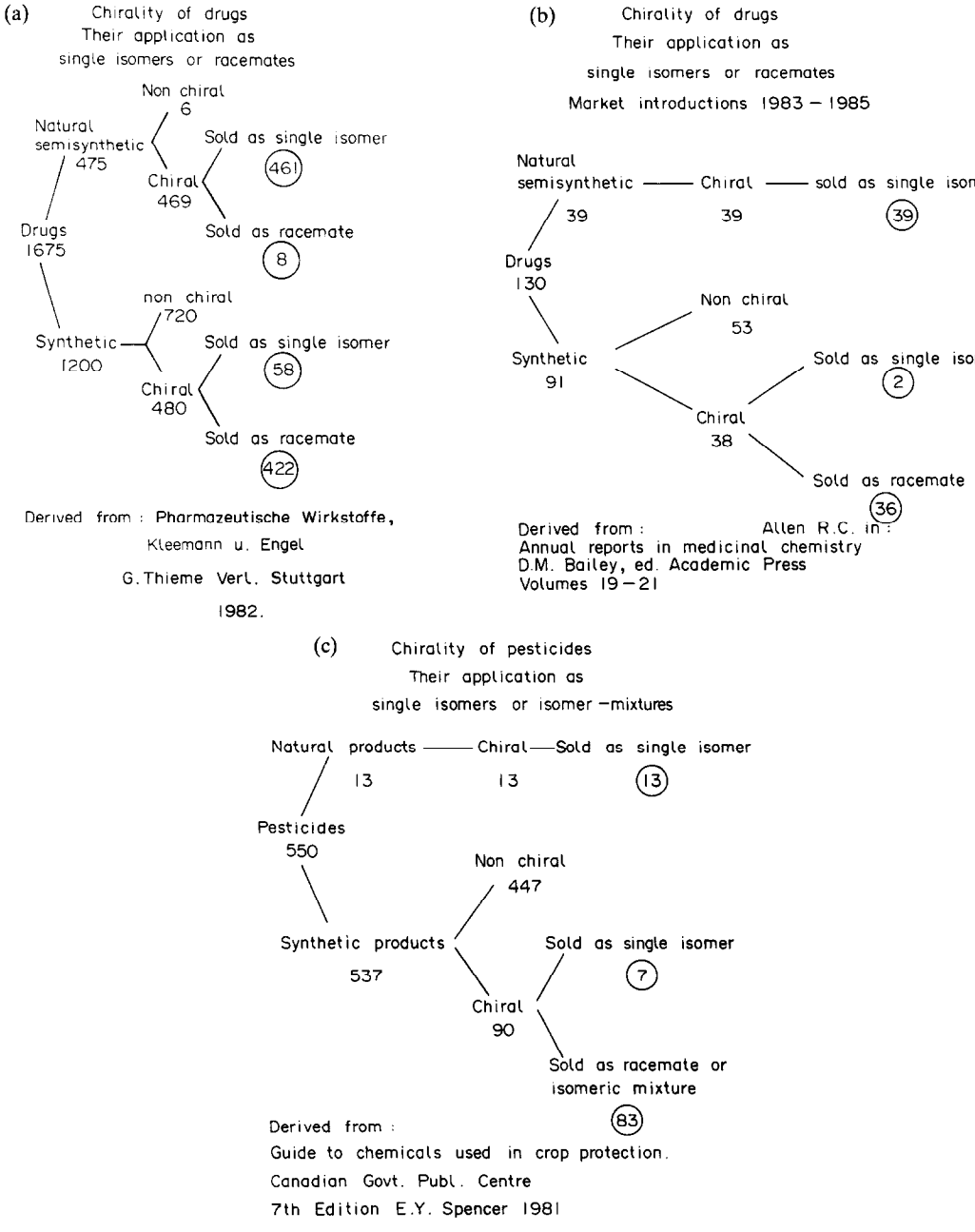


Fig. 1 (a, b, c). Chirality of drugs and pesticides and their application as single isomers or isomer-mixtures. Note: natural and semisynthetic products are mostly chiral and marketed as single isomers. The chiral agents among the synthetic compounds are mostly marketed as racemates or isomeric mixtures in general.

actualisations of the "docking" of substrates in the cleft or canyon on the active site of enzyme molecules, and the efforts to extend this approach to drugs and receptors. It is reminiscent of a hand fitting a glove. This readily evokes the picture of the right and left hand illustrating chirality and the mirror image of enantiomers. The hand–glove model taken shape in the docking manoeuvre, clearly illustrates that a close fit into the canyon of a "right-hand" type molecule is incompatible with similarly a close fit for the corresponding left-hand one. Remarkably, when stereochemistry enters the picture sophistication in medicinal chemistry vanishes (Fig. 1a–c).

STRUCTURE, ACTION AND CHIRALITY

A center of asymmetry is not necessarily located in a region of the bioactive molecule critically involved in the interaction with the receptor or enzyme. The asymmetric center in the cholinergic agent acetyl-β-methylcholine is in a critical position,

Table 1. Nomenclature and definitions proposed for stereospecificity in action

For a particular set of isomers in relation to one particular biological type of action:	
Eutomer:	isomer with higher affinity (aff_{eu})
Distomer:	isomer with lower affinity (aff_{dis})
Eudismic ratio (ER):	aff_{eu}/aff_{dis}
Eudismic index (EI):	log aff_{eu} − log aff_{dis}
(ER and EI are measures for the stereospecificity of the compound)	
For a series of chemically related chiral agents and one particular type of biological action:	
Eudismic affinity quotient (EAQ): b in equation EI = a + b log aff_{eu}	
(EAQ is a measure for the stereospecificity in a series of chemically related compounds for the particular biological effect. It usually increases with log aff_{eu}, which is known as Pfeiffer's rule)	

From Refs 4, 5, 7, 8, 10.

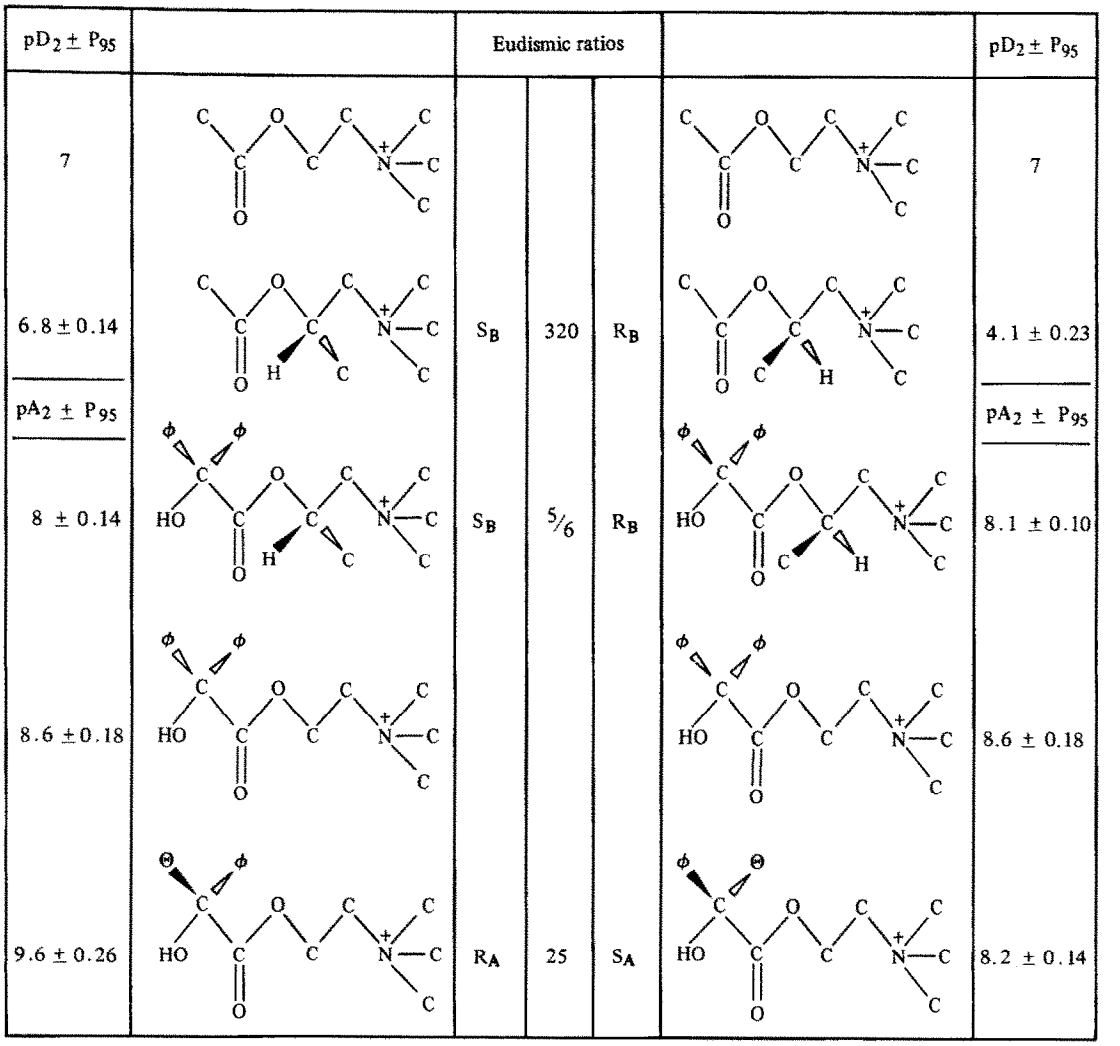


Fig. 2. Dependence of the eudismic ratio on the position of the asymmetric center in the bioactive molecule. Activity ratios of the stereoisomers of β-methylcholine and choline esters tested on the isolated gut of the rat. The high activity ratio—eudismic ratio—for the isomers of acetyl-β-methylcholine and the ratio close to one for the isomers of the benzylic ester of β-methylcholine indicate a loss of relevance of the center of asymmetry in the β-methylcholine moiety in the switch from cholinergic to anticholinergic action. The relatively high eudismic ratio for the center of asymmetry present in the anticholinergic phenylcyclohexyl-glycolic acid ester of choline indicates the relevance of the ring substituted group for the binding of this type of anticholinergic agents. pA_2 according to Arunlakshana O and Schild HO, *Br J Pharmacol* **14**: 48, 1959. B = base, A = acid. Based on data from Ref. 6.

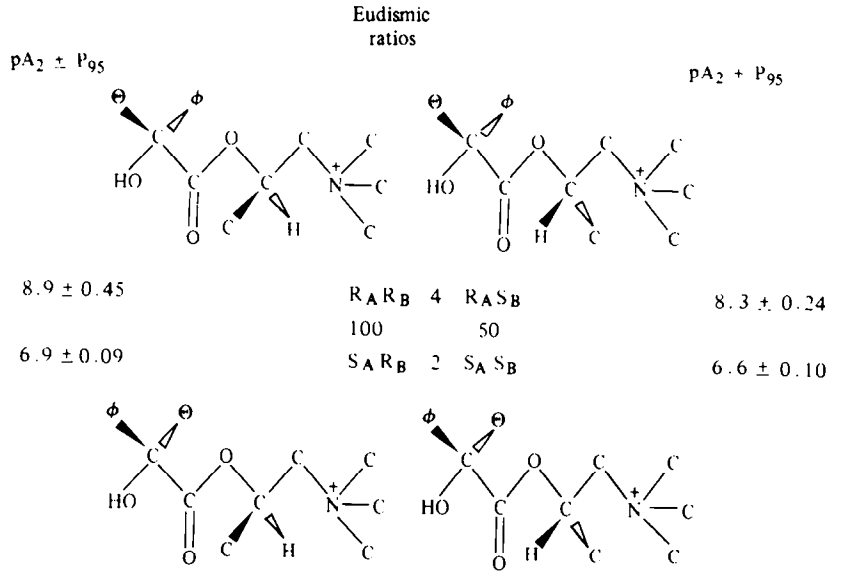


Fig. 3. Stereoisomers and biological activity of choline esters of phenylcyclohexyl-glycolic acid. The ratios for the anticholinergic action—eudismic ratios—of the four isomers of phenylcyclohexyl-glycolic-β-methylcholine tested on the jejenum of the rat. The eudismic ratios depend upon the region of the drug molecule in which the chiral center is located. This indicates that agonist and antagonist differ in their regions critical for receptor binding. For the antagonist, binding on accessory areas on the cholinergic receptor molecule close to the receptor site for acetylcholine is postulated. For abbreviations and references see Fig. 2.

its eudismic ratio (see Table 1 for nomenclature) is large (ER ± 300) (Fig. 2). Ring substitution in the acid-moiety of the molecule results in a switch to anticholinergic action. The center of asymmetry in the choline-moiety now finds itself in a noncritical position and hardly counts any more; ER is close to one. Introduction of a center of asymmetry into the substituted acid-moiety results in high ER values (Figs 2 and 3) [6, 8]. This type of anticholinergic agents mainly binds to an accessory area on the cholinergic receptor molecule, close to the site for binding the agonist. Similar relations have been reported for a variety of receptor blocking agents [8]. For a chiral compound with multiple blocking actions, the ER values differ for the different receptor types involved. For the drug butaclamol, the ER(±) is 1250 for the D_2-dopaminergic receptor, 143 for the $5HT_2$- and 8 for the $5HT_1$-serotonergic receptor, 73 for the α_1-adrenergic and 0.5 for the cholinergic (muscarinic) receptor [9, 11].

In a plot of the eudismic index (EI) as a function of log aff_{eu}, the slope of the curve which is a measure for the stereospecificity of a series of chiral compounds differs for different receptor systems and enzymes involved. In general, a very high activity implies that only very low concentrations are required for action. At such low concentrations the chance of actions on other types of receptors, and the attendant side effects, is relatively small. High activity therefore, tends to high selectivity in action. The same holds true for pairs of isomers. If aff_{eu} is very high, then there is a small chance of the distomer in the racemate being active in the same or in another sense [10]. Thus, with the development of more active and sometimes highly potent bioactive agents, selectivity and stereoselectivity in action inclines to become more pronounced.

With the concept of the three-point interaction [12] between a bioactive agent and its specific site of action, it can easily be visualised that enantiomers are essentially different compounds. In their relation to the active sites they often differ more than homologous compounds such as *N*-methyl, *N*-ethyl and *N*-propyl derivatives, or agents with para-chlorine, -bromine, or -methyl substituted phenyl-rings. Think of the left hand that does not fit the right-hand glove. Two right hands, however, which slightly differ in the length or thickness of the thumb, may both fit the same right-hand glove.

IMPLICATION OF CHIRALITY IN BIOACTIVE XENOBIOTICS

In many cases, scientists dealing with mixtures of isomers adhere to the idea that these mixtures are composed of an active isomer, the eutomer, and an inactive, and therefore negligible, isomer, the distomer. There is abundant evidence, however, for many kinds of actions of "inactive" isomers and of interactions between eutomer and distomer. As soon as enzymes, carrier molecules, specific receptors, etc. are involved, stereospecificity tends to occur. Not only may the isomers differ in the metabolic rates at which they are processed, they may even be processed along different pathways. They may show preference for different receptor types, and thus produce different actions. Almost every conceivable difference in metabolic conversion and action of enantiomers and in interaction between xenobiotic enantiomers, has been found to have materialised. Over the years, a number of surveys presenting

Table 2. Toxicity of the enantiomers and racemates of fonofos and fonofos oxon in house flies and white mice

Compound name	Number	House fly LD_{50} (μg/g)	Mouse (oral) LD_{50} (mg/kg)
Fonofos			
racemic	—	12.0	14.0
(*S*)	1	25.0	32.0
(*R*)	2	6.3	9.5
Fonofos oxon			
racemic	—	8.0	21.0
(*S*)	3	4.0	6.0
(*R*)	4	48.0	38.0

Note: to draw conclusions on structure activity relationships, one should not compare compound 1 with 3 and compound 2 with 4, but 1 with 4 and 2 with 3. The latter have corresponding configurations although they differ in their nomination.

On basis of data from Ref. 26.

ample selections of examples hereof and discussing practical consequences of chirality in drugs has appeared [7–10, 13–24].

The field of pesticide stereoselectivity will be less well known to the readers of this journal. It is as complex, as interesting, and as elucidatory as the field of drugs. There are many parallels to be shown in a few examples.

The various nomination systems for isomers, including the *R,S*-system [25], fail to give direct information on the sterical configuration determinant for the biological activity. In general, a switch in nomination is a consequence of the conventions underlying the nomination system. This does not necessarily imply a switch in the particular sterical configuration required for a specific biological action. What counts is the spatial arrangement of those groups in the molecule essential for interaction with the site of action. Table 2 shows how problems may arise in this respect [26]. The conversion by mixed function oxidase of the organic phosphate fonofos to fonofos oxon influences a number of biological parameters. The question arises, how does this biochemical conversion influence the action. At first sight, one might be inclined to compare the data of compound 1 (*S*-fonofos) with compound 3 (*S*-fonofos oxon), and of 2 (*R*-fonofos) with 4 (*R*-fonofos oxon). However, as shown in Fig. 4, in the conversion to the oxon the configuration is maintained although the nomination has changed [26]. *R*-fonofos and *S*-fonofos oxon have the configuration proper for activity. This means that to come to proper conclusions on structure–activity relationships, one has to compare compound 1 with 4, and compound 2 with 3.

In the case of large differences in or even opposite values of ER for the various components in the biological action, separation of the isomers will result in an increase in selectivity or possibly separation of the different actions. An example is paclobutrazol. The 2*R*,3*R*-enantiomer has a high fungicidal and a low herbicidal activity, the 2*S*,3*S*-enantiomer shows the reverse (Table 3) [27]. If used as a fungicide on plants, the herbicidal action is undesired. By separating the isomers, the actions can for the greater part be dissociated. An example from the drug field is propoxyphene. Both the analgesic 2*R*,3*S*-isomer Darvon® and the antitussive 2*S*,3*R*-isomer Novrad® (note the mirror image in the names) are on the market [10, 15].

As mentioned earlier, enantiomers and stereoisomers in general have to be regarded as essentially different compounds. They may follow different metabolic routes. Figure 5 [28] gives an example of "species differences" in metabolic pathways for the isomers of the profungicide triadimefon and its conversion (bio-activation) to the fungicide triadimenol. The efficacy of triadimefon changes with the fungi involved. Figure 6 [29] illustrates how the transformation of the organic phosphate prophenphos to prophenphos-*S*-oxide implies a decrease in action (bio-inactivation) for the (+)-isomer and an increase (bioactivation) for the (−)-isomer. This metabolic conversion results in a true inversion of the eudismic ratio. An interesting example of stereospecific conversion in the exposure phase is summarised in Table 4 [30] for the weedkiller fluazifop-butylester. In the soil, the inactive *S*-enantiomer of the formed acid is inverted to the active *R*-acid, while the active *R*-isomer is not changed. After sterilisation of the soil, and thus elimination of the life therein, inversion stops. As indicated, the consequences of the inversion are different for *in vitro*, post-emergence, or pre-emergence application. This biochemical inversion of inactive to active enantiomer, is comparable

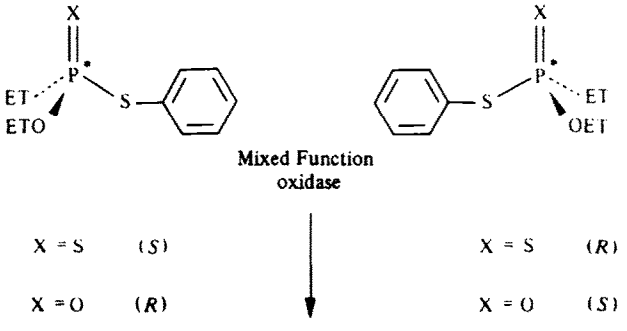
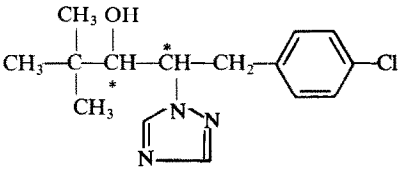


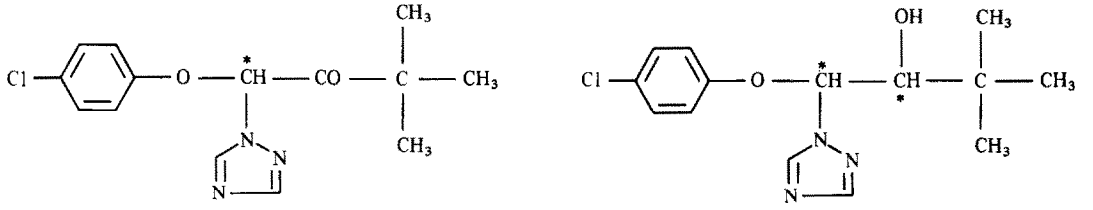
Fig. 4. Stereochemical structures of fonofos (*O*-ethyl-*S*-phenyl-ethylphosphonodithioate) and fonofos oxon (*O*-ethyl-*S*-phenyl-ethylphosphonothioate). In the conversion of the enantiomers of fonofos to fonofos oxon, the configuration is maintained although the nomination changed. On basis of data from Ref. 26.

Table 3. Biological activity of paclobutrazol stereoisomers



Compound	Fungicidal activity (cereal mildews and rust)	Plant growth regulatory activity (apple seedlings)
2*RS*,3*RS*	High	High
2*R*,3*R* (+)	High	Low
2*S*,3*S* (−)	Low	High

Note: the 2*R*,3*R*-(+)-enantiomer has a high fungicidal but a low plant growth regulatory activity. For the 2*S*,3*S*-(−)-enantiomer the reverse is true. Separation of the enantiomers implies separation of both actions. On basis of data from Ref. 27.



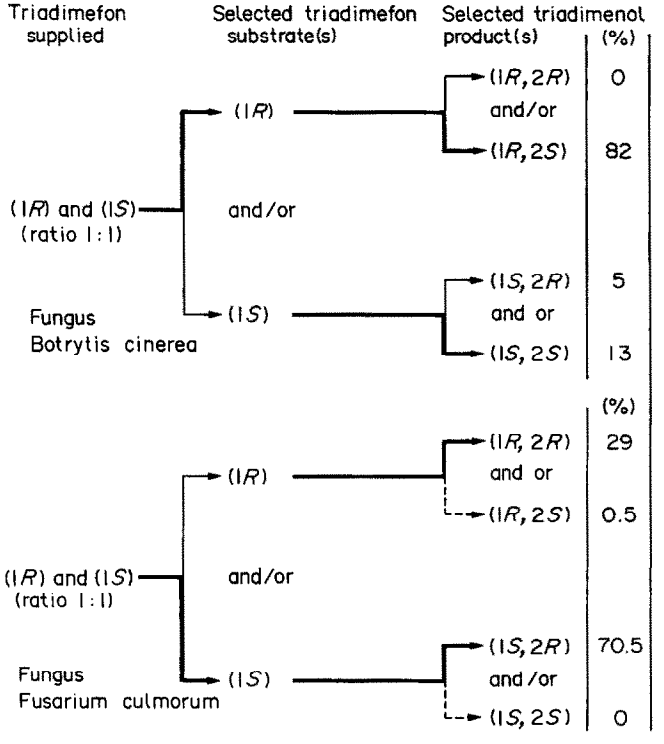


Fig. 5. Species differences in stereoselective profungicide bioactivation. The stereoselective bioactivation of triadimefon to triadimenol. The isomeric composition of the product obtained after incubation (48 hr) with fungal cultures is given. The fungicidal activity of the isomers greatly differs. For most fungi is 1*S*,2*R* ⩾ 1*R*,2*R* ≈ 1*S*,2*S* > 1*R*,2*S*. The CO-group in triadimefon constitutes a prochiral center. During the time of incubation, *Botrytis cinerea* converts 50% of triadimefon, and *Fusarium culmorum* ± 80% to the active metabolite triadimenol. Note: the substrate selectivity and product specificity and thus also the efficacy of the profungicide triadimefon differs for different fungi. On basis of data from Ref. 28.

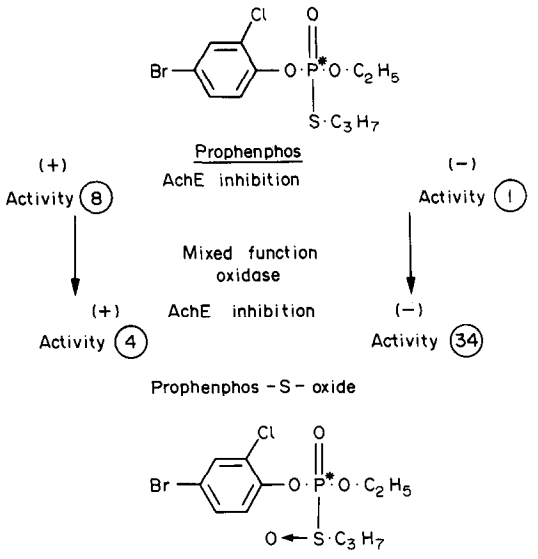
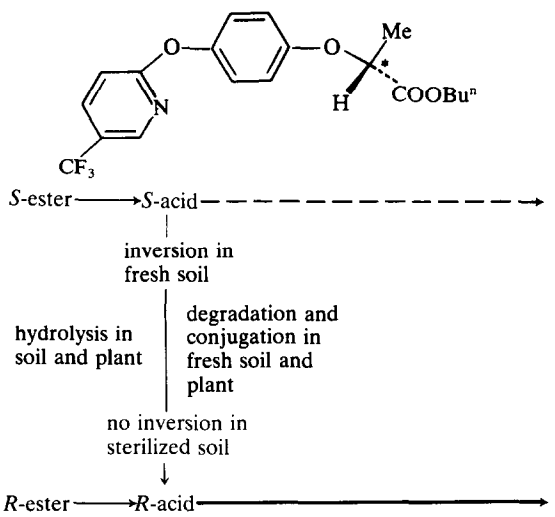


Fig. 6. Metabolic inversion of eudismic ratios. The (+)-enantiomer of prophenphos is about eight times more active than the (−)-isomer. The conversion to prophenphos-*S*-oxide by mixed function oxidase (mouse liver microsomes) leads to a reduction of the acetylcholine esterase inhibitory action with a factor two for the (+)-isomer, and an increase with a factor 34 for the (−)-isomer. The conversion switches the eutomer to the distomer position and vice versa. An inversion of the eudismic ratio takes place. Note: there is a real inversion of the eudismic ratio possibly due to a switch in the leaving group; cleavage of the P—O—phenyl linkage in prophenphos and of the P—S—propyl linkage in prophenphos-*S*-oxide. This requires another position of the organic phosphate on the enzyme. On basis of data from Ref. 29.

Table 4. Stereoselective inversion of the weedkiller fluazifop-butylester



Compound	*In vitro*	Post-emergence	Pre-emergence
Ester	*R* inactive	*R* active	*R* active
Ester	*S* inactive	*S* inactive	*S* active
Acid	*R* active	*R* active	*R* active
Acid	*S* inactive	*S* inactive	*S* active

Note: the inversion is substrate selective and product selective. On basis of data from Ref. 30.

to the inversion of the inactive *R*(−)-enantiomers of various antirheumatic agents such as ibuprofen and naproxen, to their active *S*(+)-forms which themselves remain unchanged [31, 32]. See also J. Caldwell in this issue.

For a survey on stereoselectivity in the action of pesticides and its implications, the reader is referred to the monograph *Pesticide Stereoselectivity—Biological and Chemical Problems* [10]. The examples given may convince the pharmacologist that stereospecificity in action is an aspect of chiral xenobiotics in general. There is much to be learned from related fields such as that of pesticidal action. Let us now return to pharmacology in the strict sense.

A PRE-PASTEUR ATTITUDE IN PHARMACOLOGY

There is a remarkable contrast between the advanced approaches in medicinal chemistry and the neglect of fundamental aspects of the relationship between structure, particularly sterical structure, and action in pharmacology. Illustrative examples are the "drug" labetalol and the "drug" medroxalol, presented as therapeutics with a combined α- and β-adrenergic action. Table 5 [33] gives the facts for labetalol. It is a mixture of an α-adrenergic blocking agent, a β-adrenergic blocking agent, and two isomers just constituting isomeric ballast, i.e. impurity. A comparable situation exists for medroxalol [34].

Both drugs are composed of four isomers with clearly different contributions to the various components of action. Although not documented in literature, it must be expected that these isomers also differ in the rates and possibly even the routes of metabolic conversion, such that their proportion changes with time. In this respect, the pharmacokinetic data of labetalol and medroxalol (Table 6) [35] are of particular interest. The reader is invited to figure out what the pharmacokinetic constants for the four-compound mixtures labetalol and medroxalol exactly mean. In character, they are related to something like the body weight or the age of a four-person family.

One of the questions that arises is how is it possible that in particular pharmacokineticists neglect such a relevant aspect of their field of investigation. Literature on pharmacokinetics and clinical pharmacology, including the industrial information material, is rich in information disregarding the stereochemical composite character of the many racemic drugs on the market. A search of the literature [36, 38] dealing with chiral drugs, showed that the racemic character is very often concealed and neglected, particularly with regard to pharmacokinetic constants such as half-lives, AUCs, etc. Of the articles dealing with racemates or other isomeric mixtures—about 25% of the drugs on the market are such mixtures—50% or more are deficient in the sense indicated (1986 Volumes of the *British Journal of Clinical Pharmacology, Drug Intelligence and Clinical Pharmacy* and the *Journal of Clinical Pharmacology*) [37, 39, 40]. The emphasis on this rather

Table 5. α- and β-Adrenoceptor blocking potencies of labetalol stereoisomers on isolated tissues

	Rabbit aortic strip* (α_1-adrenoceptors)		Guinea-pig left atrium† (β_1-adrenoceptors)		Guinea-pig tracheal strip† (β_2-adrenoceptors)	
	N	pA_2	N	pA_2	N	pA_2
RR-isomer	3	5.87	6	8.26	5	8.52
SS-isomer	6	5.98	4	6.43	4	<6.0
RS-isomer	3	5.5	3	6.97	4	6.33
SR-isomer	8	7.18	4	6.37	4	<6.0

The α-adrenoceptor blocking potency rests predominantly in the *SR*-isomer, the β-adrenoceptor blocking potency in the *RR*-isomer. The *SS*- and *RS*-isomers, 50% of the compound labetalol, can be regarded as practically inactive.

pA_2 calculated as described by Arunlakshana O and Schild HO, *Br J Pharmacol* **14**:48, 1959.

* Agonist used noradrenaline.

† Isoprenaline.

N = number of experiments.

On basis of data from Ref. 33.

common astereognostic bias in pharmacology in no way denies, but on the contrary sharply contrasts with the many excellent and informative studies focused on the stereochemical aspects of drug action as reviewed in Refs 7–10 and 13–24, and in the contents of this issue of *Biochemical Pharmacology*.

WHY THE EXUBERANT FLOW OF "NON-SCIENCE" IN PHARMACOKINETICS AND CLINICAL PHARMACOLOGY?

No doubt the chemists involved in the development of new bioactive agents are aware of stereospecificity and to some extent of the implications in biology. The chiral compounds they synthesize often reach the biologist under a code-number. In a later phase of the investigation, this number is replaced by some fancy name. This procedure masks the composite character of the new "agent", which has in fact to be classified as a "fixed-ratio mixture". The investigators and even more so the users of drugs and pesticides, apparently are easily misled this way. Partly as a consequence thereof, many biologists, pharmacokineticists and clinical pharmacologists operate on a pre-Pasteur level with regard to stereochemistry. This implies that, unless having been explicitly noticed, they tend to deal with isomeric mixtures as if one compound were involved. Once the mixture is marketed and the name is hammered into the physician's mind, that name stands for "the drug", "the pharmacon", "the active compound". That a clinician, asked by industry to study or evaluate their "drug" presented under a brand name while kept unaware of the chiral pitfalls he is in for, stumbles is understandable but not acceptable.

The blind spot for stereochemistry and stereoselectivity of drugs has a further cause as comes to light in a search of the various handbooks on pharmacology, pharmacokinetics and toxicology which were checked on three points: Are stereoselectivity or related terms mentioned in the index? Are implications of stereoselectivity in action discussed or elucidated? Are stereochemically biassed data such as pharmacokinetic constants of racemates avoided? The summary in Tables 7 and 8 shows that although about 25% of the products on the market are racemates or mixtures of isomers in general, in the sources of information and education for the scientists concerned, the notion of stereospecificity in the action of drugs is practically absent. Here lies an important task for editors and editorial boards of books and journals in the field of drug- and pesticide-action.

Another important factor in the generation of poor science, in the sense of waste of research money and waste of valuable time by investigators and by the readers of their publications, is the honouring of low

Table 6. Pharmacokinetics of medroxalol and labetalol

Parameters	Medroxalol	Labetalol
Peak concentration (ng/ml)	450 ± 223	327 ± 150
Time to peak (hr)	2.3 ± 0.7	1.1 ± 0.3
AUC (ng·hr/ml)	4551 ± 836*	876 ± 447
$t_{1/2}$ oral (hr)	15.6 ± 3.9	5.5 ± 5.0
$t_{1/2}$ i.v. (hr)	7.3 ± 0.8	5.2 ± 1.3
Clearance (ml/min)	948 ± 134	1560 ± 648
Bioavailability	64 ± 19*	20 ± 5

* $P < 0.05$: differences significant in the kinetics of the two drugs.

Note: medroxalol and labetalol are each composed of four isomers. Stereoisomers usually differ in their pharmacokinetic properties, such that their proportion changes with time. What is the meaning of these pharmacokinetic parameters? Compare the age and body weight of a four-person family.

On basis of data from Ref. 35.

Table 7. "Stereospecific awareness" in textbooks on pharmacology

Title	Year	Author/editor	I	II	III
Lewis's Pharmacology (1)	1980	Crossland	–	–	–
Textbook of Pharmacology (2)	1980	Bowman and Rand	+	+	–
Clinical Pharmacology (3)	1984	Girdwood	–	–	–
Medical Pharmacology (4)	1984	Goth and Vessell	–	–	–
The Oxford Textbook of Clinical Pharmacology and Drug Therapy (5)	1984	Grahame-Smith and Aronson	–	–	–
Goodman and Gilman (6)	1985	Goodman, Gilman *et al.*	–	–	–
Arzneimittelwirkungen (7)	1986	Mutschler	+	+	–
Basic Pharmacology (8)	1986	Foster	+	+	+
The Scientific Basis of Clinical Pharmacology (9)	1986	Spector	–	–	–
Topics in Clinical Pharmacology and Therapeutics (10)	1986	Maronde	–	–	–
Pharmacology (1)	1987	Rang and Dale	–	–	–
Basic and Clinical Pharmacology (11)	1987	Katzung	–	–	–

I = stereoselectivity and related terms in index.
II = discussion on implications of stereoselectivity.
III = avoidance of stereochemically biased data.
(1) Churchill Livingstone, Edinburgh. (2) Blackwell, Oxford. (3) Ballière Tindall, London. (4) Mosby, St Louis. (5) Oxford University Press, Oxford. (6) Macmillan, New York. (7) WVG, Stuttgart. (8) Butterworths, London. (9) Little Brown, Boston. (10) Springer, New York. (11) Appleton Lange, Norwalk.

Table 8. "Stereospecific awareness" in textbooks on pharmacokinetics and toxicology

Title	Year	Author/editor	I	II	III
Pharmacokinetics (1)	1975	Gibaldi and Perrier	–	–	–
Clinical Pharmacokinetics: Concepts and Applications (2)	1980	Rowland and Tozer	–	–	–
Biopharmaceutics and Clinical Pharmacokinetics (1)	1980	Notari	–	–	–
Handbook of Clinical Pharmacokinetics (3)	1983	Gibaldi and Prescott	–	–	–
Pharmacokinetic Basis for Drug Treatment (4)	1984	Benet *et al.*	–	–	–
Pharmacokinetics: Theory and Methodology (5)	1986	Rowland and Tucker	–	–	–
Casarett and Doull's Toxicology (6)	1980	Doull *et al.*	–	–	–
Introduction to Biochemical Toxicology (7)	1980	Hodgson and Guthrie	–	–	–
Toxikologie (8)	1981	Wirth and Gloxhuber	–	–	–
Environmental and Occupational Medicine (9)	1983	Rom *et al.*	–	–	–
A Guide to General Toxicology (10)	1983	Homburger *et al.*	–	–	–

I = stereoselectivity and related terms in index.
II = discussion on implications of stereoselectivity.
III = avoidance of stereochemically biased data.
(1) Marcel Dekker, New York. (2) Lea Febiger, Philadelphia. (3) Adis, New York. (4) Raven, New York. (5) Pergamon, New York. (6) Macmillan, New York. (7) Blackwell, Oxford. (8) G. Thieme Verlag, New York. (9) Little Brown, Boston. (10) Karger, Basel.

quality grant applications. Apparently, many peers, referees and reviewers evaluating grant applications in the area of pharmacology lack insight into the problems inherent to stereoselectivity. A grade A qualification for a project neglecting stereochemical aspects of the study, disqualifies the reviewer. The scarce research resources today and the time of capable researchers should not be wasted on generation of senseless data.

A final hot question: on what basis may racemates and isomeric mixtures in general be accepted as drugs or pesticides on the market? As much as it is justified to use a drug with 50% of a presumably harmless impurity because it is difficult to eliminate, so much is it reasonable to accept 50% of a presumably harmless impurity in the form of isomeric ballast. The mixture may be acceptable, but whether it is optimal is a different question. To enable proper decisions, relevant information on the properties of the separate isomers is indispensable. Industry may be expected to present full information on the stereochemistry and the implied stereoselectivity in the action of its products, including the necessary stereoselective analytical methods. Risks cannot be fully avoided, but they should be calculated risks, reduced to—also in economic perspective—the inevitable minimum.

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