ISOMERISM AND ISOMERIC DRUGS

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INTRODUCTION

The role of stereochemistry in modern drug development is currently being emphasized by both regulatory agencies and pharmaceutical industry[1-6]. A 1986 survey[7] indicates that about 50% of the 700 most frequently prescribed drugs contain at least one stereogenic centre[8]. The approval and marketing of stereoisomeric drugs, especially chiral drugs, could pose special challenges because they may exemplify dramatic differences in pharmacokinetic and pharmacodynamic properties in the chiral environment afforded by the body at the molecular level[9-24].

To address the issues relating to the safety and efficacy of stereoisomeric drugs the United States Food and Drug Administration Centre for Drug Evaluation and Research has constituted a stereoisomeric committee[25-28]. The committee is responsible for drafting guidelines and implementation of scientifically rational approach to the regulation of stereoisomeric products.

Obviously, in such a climate, it is important to have a proper grasp of various relationship among isomers. Texts and literatures to provide adequate knowledge about isomerism and isomeric drugs. But the informations are scattered in a form sometimes very difficult to retrieve. Often even in the text they remain hidden and go unnoticed. This paper is the result of an effort to consolidate, update and present the information about isomers, in particular stereoisomers, in pharmaceuticals in a convenient format. An attempt is made to illustrate each stereochemical concept by citing examples exclusively from drug molecules to make the presentation relevant to the readerships from the pharmaceutical field.

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ISOMERS : Structural Relationships

Molecules which closely resemble each other, but fail to be identical due to one difference in their structures can be designated as isomers. Recently Edwin Thall[29,30] has developed a technique called Representing Isomeric Structure (RIS) which enables one to write all isomers without duplicates.

When Isomers differ in their constitution (i.e. in the connectivity of their atoms), they are called constitutional isomers. They are sometimes further differentiated as chain isomers (or skeletal isomers), functional group isomers and positional isomers (or regio-isomers). To illustrate Constitutional isomers one can consider the relationship between β-adrenoceptor antagonist practolol and atenolol (Fig. 1), each is a racemate.

When isomers have same atom connectivity but differ in spatial orientation of their atoms (configuration), they are designated as stereoisomers. The phenomenon of existence of stereoisomers is called stereoisomerism.

STEREOISOMERS: Classification

Stereoisomers can be classified at two entirely distinct and separate levels; namely Symmetry clas-

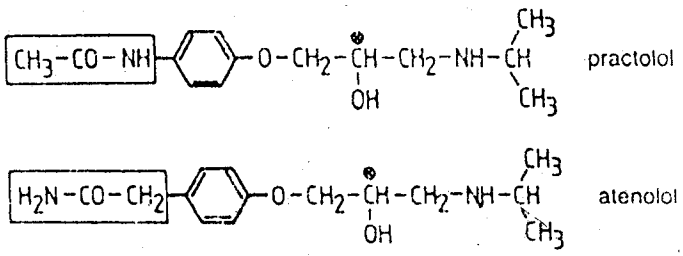


Fig. 1. Constitutional Isomers

sification and Barrier classification[31-33]. The symmetry classification of stereoisomers is based on an exceedingly simple criterion either the isomers are related as objects and mirror image or they are not. The other classification depends only on their structural features which are related to the nature and magnitude of energy barrier separating isomers (Barrier classification). In qualitative terms, high energy barrier separates configurational isomers, while the low energy barrier separates conformational isomers (conformers). The various structural relationships among isomers based on joint criteria of symmetry and energy are summarized in Fig.2.

ENANTIOMERS:

Two stereoisomers which are related to each other as object and non-superimposable mirror image are known variously as enantiomers, enantiomorphs, optical isomers or optical antipodes. This implies molecules are chiral and refers to the property of "handedness", i.e., being left-handed or right-handed. Enantiomers exhibit identical physical and chemical properties except in chiral environments.

The property of chirality is necessary and sufficient condition for the existence of enantiomeric objects. Centre of chirality and axis of chirality are the most commonly encountered structural feature that confers enantiomerism in drug molecules centre of chirality can be due to the presence of tetrahedral tetracoordinate atoms (C, N, Si, P) and pyramidal tricoordinate atoms (N,S). In pharmaceuticals, the most frequently encountered chiral tetracoordinate center is the carbon atom bearing four different substituents. A classical example of a drug with a chiral phosphorous moiety is the antineoplastic agent cyclophosphamide. The sulfur atom of nonsteroidal antiinflammatory sulindac (Fig.5a) bears four different groups (one being a pair of electrons), and hence is chiral.

The chirality of organic molecules is described by the Cahn- Ingold-Prelog system[34-38]. According to this system enantiomers are classified as 'R' (right from the Latin word 'rectus') or 'S' (left from the Latin word 'sinister') based on the spatial orientation around the chiral atom. The adrenergic agent Epinephrine is an example for a drug containing a single stereogenic centre. The maximum number of enantiomers for a chiral drug is computed by the formula 2^n where n is the number of stereogenic centres. Accordingly, Epinephrine exists in two enantiomeric forms. One of the chiral twins has an absolute configuration 'S' while its mirror-image twin has 'R' absolute configuration. Note that enantiomers have inversion of configuration at every chiral centre in enantiomeric pairs.

When a chiral compound exists as equal proportions of two enantiomers it is referred to as racemic mixture, racemic modification or racemate [symbolized by (±); R,S- or d,l-]. They are optically inactive because of external compensation. Any process that converts a single enantiomer to a recemate is called racemisation. Racemates are usually produced from synthetic process that do not favor the production of one enantiomer over another. As a consequence, a large proportion of the synthetic drugs marketed today are racemates[39-40].

Racemization can also result from inversion of labile chiral centres. Some of the benzodiazipines, oxazepam, lorazepam, and temazapam are subject to racemization in aqueous solution[41,42]. Separation of racemate into its enantiomers is called resolution. Single enantiomers are usually obtained from biologically derived starting materials or through special synthetic strategy like asymmetric synthesis[43-46].

The other structural feature that can cause enantiomerism is axis of chirality. There are two type of compounds with an axis of chirality; the allenes[47,48] and the highly ortho- substituted biphenyls[49].

Allenes are compounds whose molecules contain the following double bond sequence, ——Ç =====C======Ç———. The special geometry of allenes, with the substituent pattern abC = C=Cba, a≠b, enables it to exist in two en-

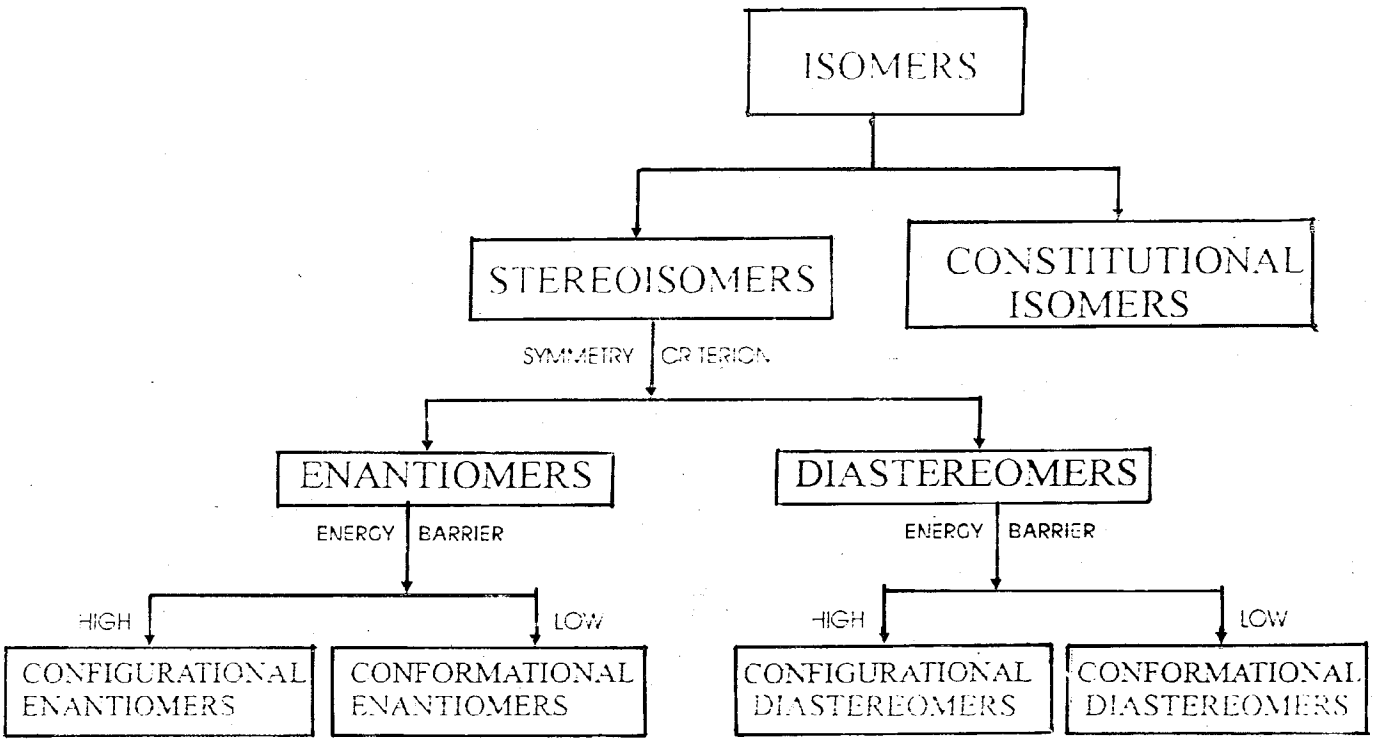


Fig.2. Isomers: Structural Relationships

antiomeric forms. The natural antibiotic mycomycin[50] (Fig. 4) is a typical example of enantiomeric allenes.

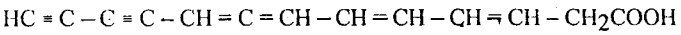


Fig.4 Enantiomeric allenes: Micomycin

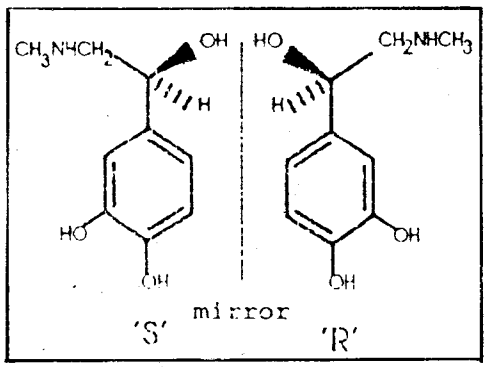


Fig.3. Enantiomers of Epinephrine.

DIASTEREOISOMERS

Diastereoisomers are stereoisomers that are not related as an object and its mirror image. They could be of two categories based on the energy barrier namely configurational diastereomer (high energy) and conformational diastereomer (low energy).

Configurational Diastereomers

Structural patterns like carbon-carbon, carbon-nitrogen, nitrogen-nitrogen double bonds and cyclic

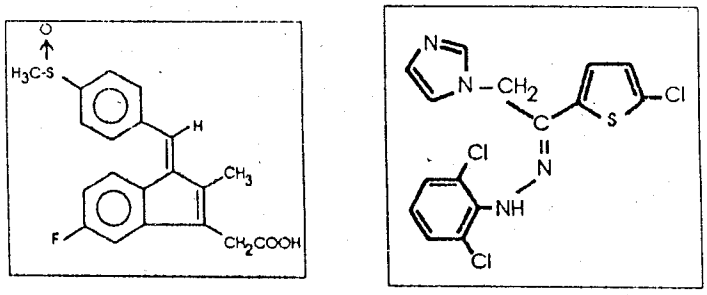
systems can generate configurational diastereoisomerism. Depending on the gross structure the molecule may be chiral or achiral.

Isomerism at double bonds : π - **diastereomers**

Diastereoisomerism about double bonds are usually designated as geometric isomerism or cis-trans isomerism[51]. In fact the term π - diastereoisomerism is more preferable since it conveys the chemical origin and correct description of the stereoisomerism. It also avoids any confusion with the cis-trans isomerism (also referred to as σ-diastereoisomerism) exhibited by cyclic systems where no double bonds is involved[52,53]. However, this terminology is used very rarely.

When the four groups attached to the double bond of a molecule are different, it is not convenient to use cis-trans nomenclature. The (E-Z) system[41,54,55] based on priorities of groups in the Cahn-Ingold-Prelog convention is the best and unambiguous way of notating two such diasteroisomers. That isomer which has the two highest ranking groups, based an sequence rules, on the same side of the double bond is called (Z) [from the German word Zusammen, meaning together] and other isomer is designated (E) [from the German word entgegen; meaning opposite].

π - diastereoisomerism due to carbon-carbon double bond is very common. A typical example is the antiinflammatory analgesic agent sulindac (Fig.5a), which has Z configuration at C=C bond and is marketed as its racemic Z isomer. Other clinically useful examples of π-diastereoisomers include the antidepressants zimilidine and doxepin, the non steroidal synthetic estrogen Diethylstilbestrol, antiestrogen tamoxifen, neuroleptic tiotixene and the antihistaminic triprolidine. π-diastereoisomerism due to carbon-nitrogen double bond is a rare phenomenon among pharmaceuticals although the antifungal agent zinoconazole shown in figure 5b which has an E configuration is an example.



(a) Sunlindac (b) Zinoconazole

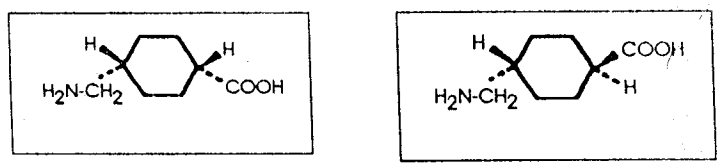
Fig.5 π-diastereoisomers

Isomerism at cyclic system: σ - **diastereomerism**

Cyclic system also offer energy barrier sufficient to produce configurational isomers.[56] In simple case of disubstituted monocylic systems, cis-trans isomerism exist provided that two substitutents are not geminal (i.e like atoms attached to the same atom in a molecule). The hemostatic agent tranexamic acid (Fig. 6) and monoamine oxidase inhibitor tranylcypromine display cis-trans isomerism.

Conformational diastereomers

Another kind of diastereoisomerism, sometimes designated as conformational diastereoisomerism occurs in molecules containing two or more chiral centers. Depending on the over all structure conformational diasteromers may be chiral or achiral. The number of possible stereoisomers varies depending whether the molecule is constitutionally unsymmetrical (non identical centres of chirality) or constitutionally symmetrical.



cis- trans-

Fig.6: cis-trans isomer: Tranexamic acid

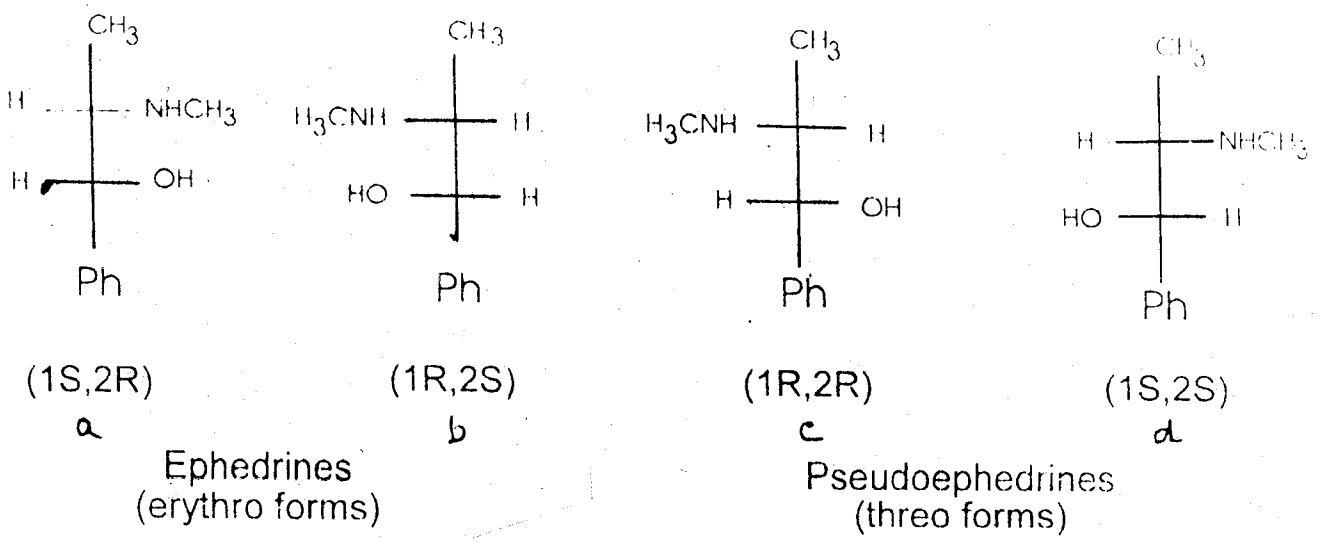


Fig. 7. Conformational Diastereomers : Ephedrine & Pseudoephedrine: Constitutionally unsymmetric molecule

An acyclic, constitutionally unsymmetrical molecule can exist as 2^n stereoisomers which are enanatiomeric in pairs. Adrenergic agent ephedrine and antibacterial chloramphenicol are good examples with n=2. Ephedrine contains two chiral centres and can exist in four optically active forms. Figure 7 depicts Fischer Projections of the stereoisomers of Ephedrine and Pseudoephedrine. The erythro pair (like groups on the same side) is called ephedrine (a,b) and threo pair (like groups on the opposite side) is called pseudo ephedrine (c,d)[57]. There exists a diastereoisomeric relationship between any of the erythro and threo isomer because out of the two stereogenic centres, the configuration at one centre is retained and the other opposed[58].

In a symmetrically substituted molecule, the chiral centre equidistant from the geometrical centre of the molecule are identically substituted. The non-steroidal estrogenic compound meso-hexestrol and the antitubercular agent mesoethambutol.[59,60] are examples worthy of special mention (Fig.8). Both are constitutionally symmetrical acylic molecule where n is even.

On paid of enantiomer is (R,R) and (S,S). The second pair of enantiomers (R,S) and (S,R) does not exist since they are superimposable. Hence achiral. This is indicated by the presence of a plane of symmetry. The achiral stereoisomer is called the meso-form, and it holds a diastereoisomeric relationship with the optically active stereoisomers. Thus ethambutol exists as 2 + 1 stereoisomers.

Diastereoisomers differing in configuration at only one (of several) chiral center are designated epimers. The inversion of configuration at one chiral center (eg. RSR → RRR) is called epimerisation. A number of drugs with two or more chiral centers are known to undergo epimerisation. The broad spectrum oxalactam antibiotic latamoxef (moxalactam) is an example of a drug which undergoes spontaneous epimerisation in aqueous solution[61]. To cite another example, cholinergic agonist Pilocarpine, with absolute configuration 2S:3R (Fig.9), epimerizes to (2R:3R)-isopilocarpine by inversion at C (2)-chiral center[62].

Epimers differing in configuration at C -1 are called anomers, a term commonly used in carbohydrate chemistry to indicate the two epimers at the hemiacetal or acetal carbon of a sugar in the cyclic form. For example, α-Glucose and β-Glucose are anomers.

CONFORMATIONAL ISOMERS:

Stereoisomers that can be rendered completely superimposable by the relatively facile rotation about

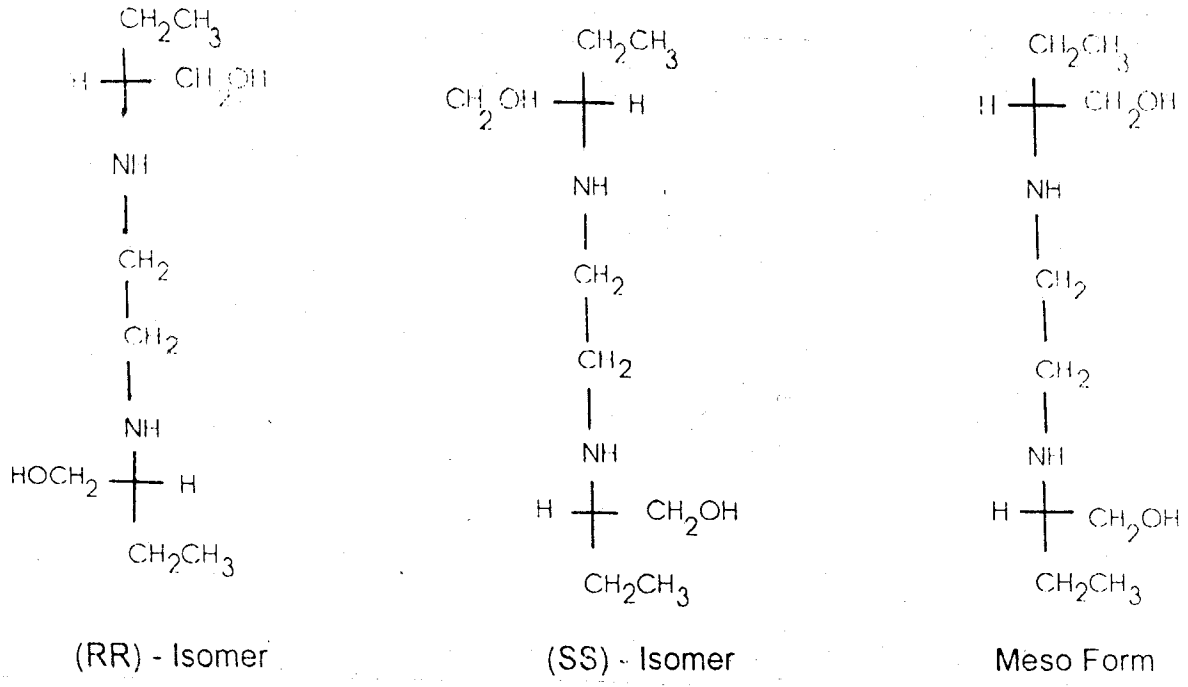


Fig.8. Conformational Diastereomers : Ethambutol; Constitutionally symmetric molecule

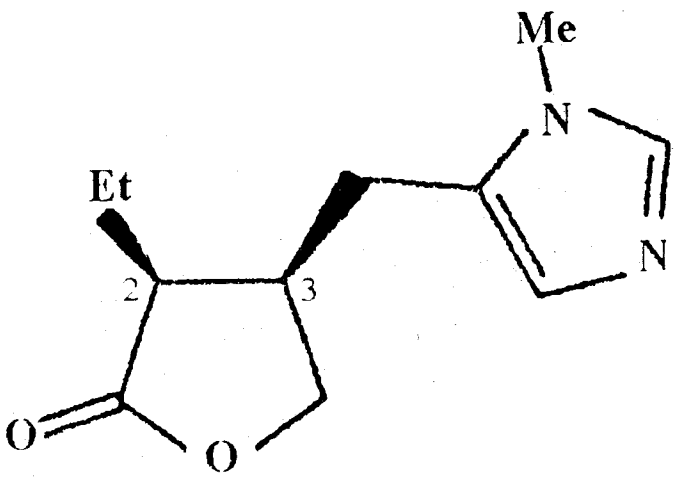


Fig.9. Epimers: Pilocarpine

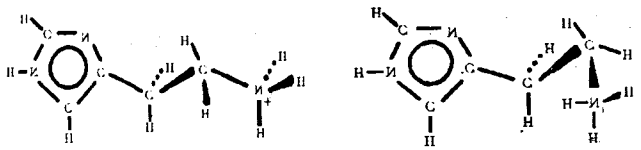


Fig.10. Conformational isomers: Histamine

the σ bonds are called conformational isomers. The term is used to any one of the infinite number of arrangements of atoms in space that result from the rotation of any of the single bonds in the molecule. It is important to realize that conformational isomers are different three-dimensional arrangements in space of the atoms of a single compound. Conformational isomer, are also referred to as conformers, rotamers (rotomers) or torsional single bond isomers. Open chain neurotransmitters epinephrine, acetyl choline, dopamine and histamine are conformationally flexible molecules[63-66]. The two nearly equally preferred but significantly different conformations for histamine are presented in Fig. 10. Conformational flexibility of the neurotransmitters has been used to explain the ability of these biomolecules to activate multiple subtypes of receptors.

Conformational isomerism is believed to be of great significance for drug receptor interactions. The catecholamine, norepinephrine presumably interact with their receptors in the anti staggered conformation (Fig.11).

As pointed out earlier, Suitably ortho substituted biphenyl systems exhibit enantiomerism. These molecules are chiral with respect to an axis. The chirality

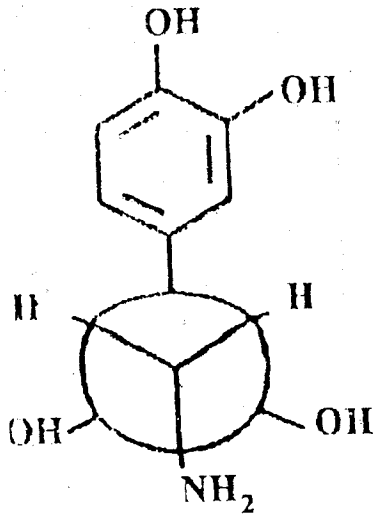
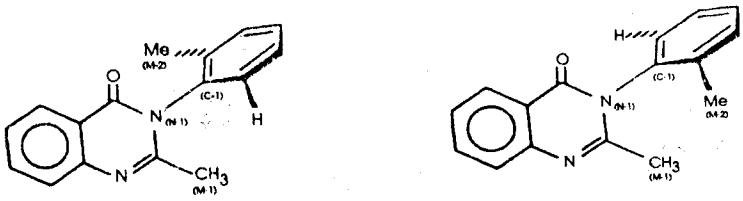


Fig.11. Pharmacophoric conformation: Norepinepherine



(+) (-)

Fig.12. Atropisomers: Methaqualone

is due to impeded rotation around this axis and is labeled as atropisomerism (configurational enantiomerism). The concept of biphenyl atropisomerism is readily extended to systems which differ formally in structure but in which stereochemical requirement for atropisomerism closely resemble those in optically active biphenyls. The hypnotic methaqualone[67,68] and the antifertility agent gossypol demonstrate atropisomerism[69,70]. The structure of the enantiomeric pairs, referred to as atropisomers, of methaqualone are presented in the figure 12. In this molecule the chiral axis is between the nitrogen atom (N-1) and the phenyl ring (C-1).

CONCLUSION

Isomerism is a fundamental concept in organic chemistry which refer to different types of relationship between molecular species. The importance attached to issues involving isomeric drugs is evident from the survey of recent literature. The rapid progress made in the field of drug stereochemistry and the need to describe and distinguish various stereochemical concept, necessitated the growth of an extensive nomenclature. A detailed treatment of stereochemical nomenclature may be found in literatures and organic stereochemistry texts[71,72]. Molecular models can be employed to examine and understand isomeric molecules. For an interesting article in this area the reader is referred to an article by Professor Harkrishan Singh and co-workers[73]. Today, several PC-molecular modeling and molecular graphics software packages are available in the market that provide excellent learning environment for studying stereoisomers[74-77]. Various aspects of isomerism and stereochemistry influence drug activity particularly in the context of drugs binding to enzymes or other proteins. Finally, author emphasizes the need to recognize stereochemical relationships between isomeric drug molecules, which is essential to explore the physical, chemical and biological implications.

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