Chapter 31. Enantioselectivity in Drug Metabolism

Lawrence K. Low and Neal Castagnoli, Jr., Dept. of Pharmaceutical Chemistry, University of California, San Francisco, California 94143

Introduction - The inherent asymmetry of biological systems leads to diastereomeric interactions between small chiral molecules and the binding sites of biomacromolecules. These interactions contribute to the stereochemical differences in pharmacological activity observed for a variety of asymmetric drugs.[1-3] Such diastereomeric interactions may occur with membrane components involved in transport,[2,4,5] with receptors,[6,7] and with enzymes responsible for the stereoselective biotransformation of drugs and other xenobiotics. As pointed out in a previous review by Jenner and Testa,[8] stereoselective biotransformations often are difficult to delineate in vivo since absorption, distribution and excretion may contribute to the overall disposition of chiral molecules. Therefore, in reports where enrichment of one enantiomer is seen in plasma, urine or tissue, caution must be exercised in assessing the contribution of metabolism.

Three stereochemical metabolic events have been defined:[8,9] (1) Substrate stereoselectivity in which the two enantiomers of a chiral molecule are differentially metabolized; (2) Substrate-product stereoselectivity in which a prochiral center of a chiral molecule is metabolized preferentially to one of the two possible diastereomers; and (3) Product stereoselectivity in which a prochiral center of a symmetric molecule is metabolized preferentially to one of the two possible enantiomers. The present chapter is primarily concerned with recent reports (1974-1977) on substrate dependent enantioselective metabolism of chiral CNS agents, autonomic and cardiovascular agents, and miscellaneous drugs and xenobiotics.

CNS Agents

Narcotic Analgesics - The greater analgesic potency of R(-)-methadone (1) compared to its S(+)-enantiomer is reported to result from stereochemical differences in affinity for the opiate receptor rather than from stereoselective differences in disposition or metabolism.[10,11] This conclusion conflicts with several studies which report the enantioselective metabolism of either S(+)-1 [8] or R(-)-1 .[12] Differences in the biotransformation of the enantiomers of both isomethadone (2) and α-acetylmethadol (3) have been reviewed.[8]

In rats, the pharmacologically active 2S,3R(+)-propoxyphene (4) undergoes slower N-demethylation and binds to liver microsomes less tightly than does (-)-propoxyphene.[13] Higher plasma levels, slightly longer half-life, and slower tissue uptake have been observed for the (+)-enantiomer after oral adminstration of racemic propoxyphene in dogs.[14] Enantiomeric interactions[15,16] have been suggested to be responsible for the enhanced analgesic activity and higher plasma and brain levels of (+)-propoxyphene when racemic propoxyphene is adminstered compared to the corresponding values obtained with (+)-propoxyphene alone.[16]

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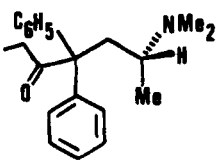
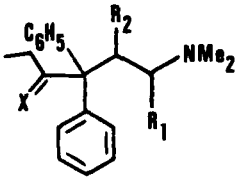
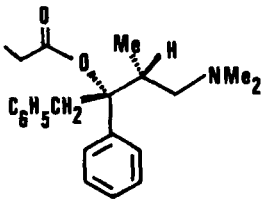


R(-)- 1



2 R_1=H, R_2=Me, X=O

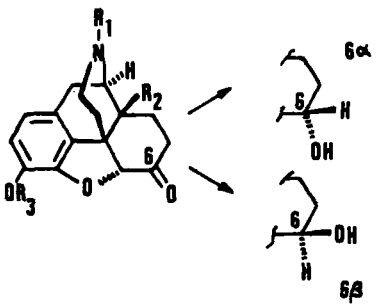
3 R_1=Me, R_2=H, X= 

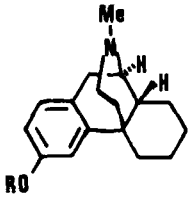


2S,3R(+)- 4

Conflicting results concerning the enantioselectivity of the N-,O- and N,O-dealkylation pathways of opiates have been discussed.[8] Recent studies investigating the reduction of the 6-keto function in various dihydromorphinones and dihydrocodeinones indicate marked species variations in the stereoselective formation of the two possible diastereomeric 6α- and 6β-hydroxy metabolites.[17-19] For example, naloxone (5) and naltrexone (6) are metabolized in the chicken to 6α-naloxol and 6α-naltrexol, respectively, whereas in the rabbit, they are metabolized to the corresponding epimeric 6β-metabolites. In man, naltrexone is primarily reduced to 6β-naltrexol.[19] Different soluble hepatic reductases appear to be responsible for the observed product stereoselectivity.[17,18] Other substrates undergoing 6-keto reduction such as oxymorphone (7), hydromorphone (8), oxycodone (9), and hydrocodone (10) also demonstrate species dependency.[17]

	R_1	R_2	R_3
5	allyl	OH	H
6	CH_2-cyclopropyl	OH	H
7	Me	OH	H
8	Me	H	H
9	Me	OH	Me
10	Me	H	Me





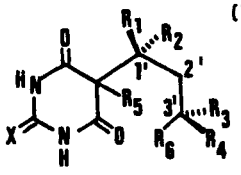
[-]-11 R=H

[-]-12 R=Me

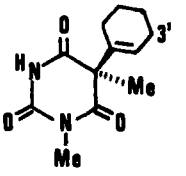
N-Methylmorphinan derivatives also show differences in the metabolism of their enantiomers. The analgesically active (-)-3-hydroxy-N-methylmorphinan or levorphanol (11) is N-demethylated to a greater extent than its (+)-isomer, dextrorphan but undergoes less extensive glucuronidation or excretion compared to the (+)-enantiomer.[21] The O-methylated derivative of (-)-11, levomethorphan (12), also undergoes more rapid N-demethylation than its inactive (+)-isomer, dextromethorphan.[13] Enantiomeric interactions have been reported whereby dextromethorphan enhances and prolongs the analgesic activity of its enantiomer, levomethorphan.[15]

Barbiturates and Related Compounds - The more active S(-)-pentobarbital (13) undergoes stereoselective hydroxylation at the prochiral C-3' atom

giving a 5:1 ratio of the two possible diastereomeric (1'S,3'R) and (1'S, 3'S) alcohols (14). In contrast, the R(+)-enantiomer is less selectively hydroxylated to its pair of diastereomeric alcohols {1:1 ratio (1'R,3'S) and (1'R,3'R)}.[22] Kinetic studies suggest the involvement of two enzymes.[23] S(-)-Thiopental (15) also shows remarkable stereoselective 3'-hyroxylation.[24] Comparative studies of the individual enantiomers of thiopental (15) and thioamylal (16) demonstrate no apparent stereoselective difference in their metabolism to the carboxylic acid derivatives (17) and (18).[24]



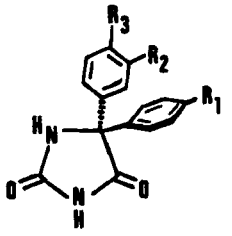
	R_1	R_2	R_3	R_4	R_5	R_6	X
S(-)-13	Me	H	H	H	Et	Me	O
(1'S,3'R)-14	Me	H	OH	H	Et	Me	O
15	Me,H	H	H		Et	Me	S
16	Me,H	H	H		allyl	Me	S
17	Me,H	H	H		Et	COOH	S
18	Me,H	H	H		allyl	COOH	S



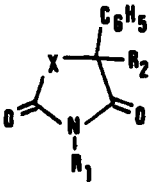
R(-)-19

Preferential metabolism (primarily 3'-hydroxylation and 3'-keto formation) of the enantiomers of hexobarbital (19) has been reviewed.[8,25] In man[26] and mouse[27] the less active R(-)-isomer is metabolized more rapidly whereas the opposite is true in the rat.[27,28] Kinetic and binding spectral studies suggest that the preferential binding of S(+)-19 in the rat and R(-)-19 in the mouse to microsomal enzymes might be responsible for the enantioselective biotransformation observed in each species.[27,29] Recent reports on N-hydroxylation of amobarbital[29a] and pentobarbital[29b] have not addressed the question of product stereoselectivity which might arise when one of the two nitrogens is preferentially hydroxylated.

Biotransformation of phenytoin or 5,5-diphenylhydantoin (20) in man and dog reveals striking stereoselectivity in aromatic hydroxylation of the two prochiral phenyl rings.[30,31] In man, highly preferential 4-hydroxylation of the pro-S phenyl ring accounts for the 10:1 ratio of S(-)-21 to R(+)-21 excreted in urine (as their β-glucuronide conjugates). In contrast, dogs stereoselectively carry out 3-hydroxylation of the pro-R phenyl ring to yield R(+)-22 although some 4-hydroxylation is observed. The overall ratio of R(+)-22/S(-)-21/R(+)-21 found in dogs is 18:2:1.[31]



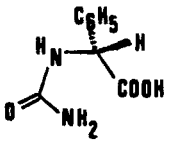
	R_1	R_2	R_3
20	H	H	H
S(-)-21	OH	H	H
R(+)-21	H	H	OH
R(+)-22	H	OH	H



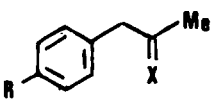
	R_1	R_2	X
23	Me	Et	NH
24	Et	H	NH
25	H	H	NH
26	Me	H	CH_2
27	Me	Me	CH_2

The enantioselective biotransformations (N-dealkylation or hydrolysis) of chiral hydantoins, mesantoin (23), ethotoin (24), 5-phenylhydantoin (25) and the chiral succinimide, phensuximide (26) have been discussed in detail previously.[8,9,32] More recent studies report enantiomeric differences in the N-demethylation of methsuximide (27).[33] The metabolism of racemic 5-phenylhydantoin (25) to only R(-)-2-phenylhydantoic acid (28) has been shown to be a consequence of stereospecific hydrolysis by a dihydropyrimidinase enzyme and spontaneous in vivo racemization of S(+)-25.[34,35]

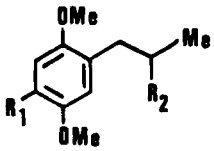
Amphetamine and Related Compounds - The stereoselective metabolism of amphetamine (29) and related compounds remains complex and controversial.[8,36] The species variation in stereoselective biotransformation of amphetamine must be appreciated.[8] Recent studies reveal that rabbit liver microsomes metabolize R(-)-29 more rapidly {to N-hydroxyamphetamine (30) and 1-phenyl-2-propanol (31)} than its active S(+)-enantiomer in separate incubations.[37,38] However, racemic amphetamine is metabolized at the same rate as S(+)-29 and shows enrichment of metabolites 30 and 31 derived



R(-)-28



	R	X
29	H	NH_2, H
30	H	NHOH, H
31	H	OH, H
32	OH	NH_2, H
33	H	N-OH



	R_1	R_2
34	Me	NH_2
35	COOH	NH_2
36	Me	NHOH

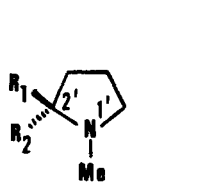
from S(+)-29. This reversal in stereoselectivity indicates that S(+)-amphetamine or one of its metabolites is inhibiting the metabolism of R(-)-amphetamine. Similar enantiomeric interactions may be occurring in the biotransformation of R(-)- and S(+)-29 to their corresponding p-hydroxylated metabolites 32 in rats.[39,40] Pharmacokinetic studies indicate that S(+)-amphetamine ($t_{1/2}$ 13-15 hrs) is cleared faster from the plasma than its R(-)-enantiomer ($t_{1/2}$ 24-30 hrs) in man after oral administration of individual isomers or racemate.[41] Enantioselective metabolism of R(-)-N-hydroxyamphetamine (30) to the propanol 31 and oxime 33 has also been reported.[38] Thermodynamic aspects of enantioselective metabolism of N-alkylamphetamine derivatives have been reported.[42]

Stereochemical studies on the metabolism of the psychotomimetic amine (±)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (34) show that the pharmacologically less active S(+)-34 is metabolized more extensively (aromatic C-4 methyl oxidation to 35, O-demethylation and oxidative deamination) than R(+)-34 in rabbits.[43-47] An exception involves N-hydroxylation to 36 which is enantioselective for the R(-)-isomer.[44] In contrast

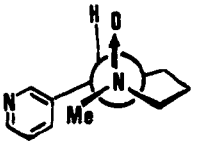
to the enantioselectivity observed with racemic 34, recent studies (no product analysis) show that the individual enantiomers are metabolized at the same rate.[48] These results have been interpreted in terms of an enantiomeric interaction in which the S(+)-isomer or its derived metabolite(s) is inhibiting the metabolism of the R(-)-antipode. Rats dosed with racemic 34 excrete more of the R(-)-enantiomer in the urine.[49]

Miscellaneous CNS Agents - N-Oxidation of the two enantiomers of nicotine show no substrate stereoselectivity but does exhibit marked product stereoselectivity.[8,50] Naturally occurring S(-)-nicotine (37) and its R(+)-enantiomer 38 are oxidized preferentially to the 1'R-N-oxides 39 and 40, respectively.

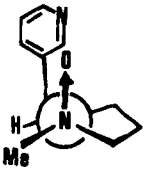
Although enantioselective metabolism and disposition are unlikely to explain the thirteen-fold greater pyschotomimetic activity of naturally occurring (-)-Δ^1-tetrahydrocannabinol (41) over (+)-41, they may account for the 1.8-fold higher brain levels (in mice) of the 7-hydroxylated metabolite 42 derived from (+)-41.[51]



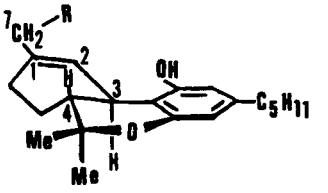
	R_1	R_2
S(-)-37	H	3-pyridyl
R(+)-38	3-pyridyl	H



39 (1'R,2'S)



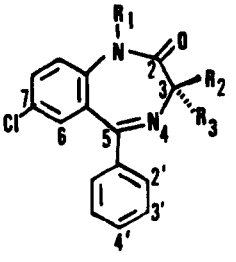
40 (1'R,2'R)

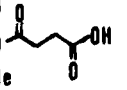


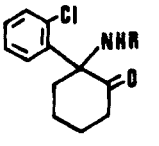
3R,4R(-)-41 R = H

42 R = OH

Microsomal hydroxylations of diazepam (43) and desmethyldiazepam (44) proceed stereoselectively at the prochiral C-3 carbon atom to yield optically active (S)-N-methyloxazepam (45) and S(+)-oxazepam (46), respectively.[52] Since the 3-hydroxylated metabolites are pharmacologically active,[53] the stereochemistry about C-3 may be important in the CNS activity of benzodiazepine enantiomers. The enhanced stereoselectivity observed for the hydrolysis of S(+)-oxazepam hemisuccinate (47) compared to its R(-)-enantiomer may account for the greater CNS activity of the (+)-iso-

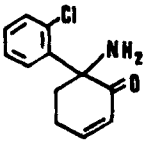


	R_1	R_2	R_3
43	Me	H	H
44	H	H	H
45	Me	H	OH
46	H	H	H
47	H	H	
48	Me	H	Me
49	H	H	Me



50 R = Me

51 R = H



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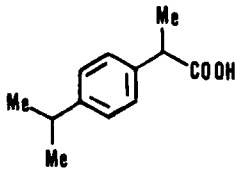
mer.[54,55] In a series of optically active 3-substituted 1,4-benzodiazepin-2-ones, the enantiomers with the (3S)-configuration (e.g. 48 and 49) appear to possess greater pharmacological activity than the essentially inactive (3R)-enantiomers.[56] Preferential aromatic hydroxylations (at C-3' and C-4') are observed for S(+)-48 and S(+)-49.[57] Other metabolic pathways for 48 and 49 (e.g. N-demethylation and C-3 hydroxylation) display no enantioselective differences.[56,57] Recent reports indicate that the (+)-enantiomers of some benzodiazepines have 100 to 200-fold greater affinity for a "CNS benzodiazepine receptor" than do their (-)-enantiomers.[7]

Stereoselective differences in the metabolism of the two enantiomers of the dissociative anesthetic agent ketamine (50) have been observed in rats[58] and mice.[59] Plasma pharmacokinetic studies indicate enantioselective N-demethylation of (+)-ketamine to the corresponding norketamine (51) and stereoselective conversion of (-)-ketamine to the cyclohexenone metabolite 52.[59]

Differential disposition of the enantiomers of the non-steroidal anti-inflammatory agents, ibuprofen (53) and cicloprofen (54) is complicated by observations that the (-)-enantiomers of both 53 and 54 can undergo metabolic inversion of configuration to the corresponding (+)-enantiomers. This novel unidirectional bioinversion may account for the predominance of (+)-53 in urine and plasma after adminstration of racemic or (-)-ibuprofen.[60,61] Similar isomerizations have been reported for (±)- and (-)-cicloprofen leading to accumulation of the (+)-enantiomer.[62,63] Prefer-



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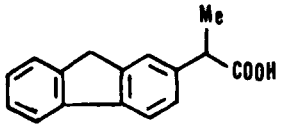

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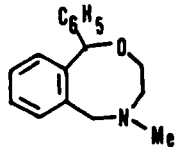

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ential elimination of the (-)-isomer is not responsible for these effects.[64] Instead, (+)-cicloprofen appears to be metabolized and excreted more rapidly than its (-)-antipode.

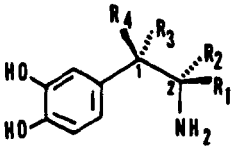
Stereoselective microsomal oxidation of the two enantiomers of nefopam (55) (an antidepressant and muscle relaxant) has been examined and indicate that the (+)-isomer is more rapidly N-demethylated.[65] Kinetic studies demonstrate that one enzyme is demethylating both enantiomers and indicate inhibition of metabolism at high substrate concentrations.

Autonomic and Cardiovascular Agents

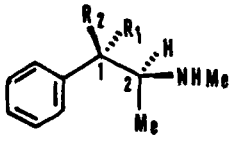
Enantioselective transport, uptake and metabolism of endogenous catecholamines and adrenergic drugs have been reviewed.[2] Studies with the antihypertensive drug, α-methyldopa, have demonstrated enantioselective transport of the active S(-)-isomer 56 into rat brain and its metabolic

conversion to the false neurotransmitters S(+)-α-methyldopamine (57)[4] and 1R,2S(-)-α-methylnorepinephrine (58).[2] Previous reviews[2,8] have emphasized the importance of stereospecific transport and decarboxylase activity in contributing to the observed differences in absorption and metabolism of S(-)-dopa (59) and its enantiomer.

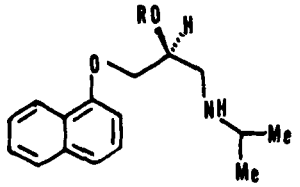
Stereoselective differences in the biotransformation and excretion of the enantiomers of ephedrine have been reported in rabbits.[66] The more active 1R,2S(-)-60 is more rapidly oxidized but more slowly excreted than the (+)-enantiomer. The 1S,2S(+)-isomer, pseudoephedrine (61) is N-demethylated more rapidly that its (-)-antipode.[8] In rats, (-)-ephedrine is ring hydroxylated but (+)-ephedrine is not.



	R_1	R_2	R_3	R_4
S(-)-56	COOH	Me	H	H
S(+)-57	H	Me	H	H
1R,2S(-)-58	H	Me	H	OH
S(-)-59	COOH	H	H	H



	R_1	R_2
1R,2S(-)-60	H	OH
1S,2S(+)-61	OH	H



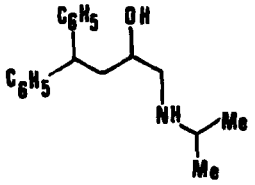
S(-)-62 R = H

63 R = glucuronyl

Differences in the disposition of the active S(-)-62 enantiomer of the adrenergic β-blocker, propranolol, and its R(+)-enantiomer have been reported.[67-69] Slower metabolism, longer half-life, more O-glucuronide (63) formation, and more stereoselective uptake have been noted for the S(-)-enantiomer. Numerous metabolites of racemic propranolol have been characterized[70,71] but enantioselective differences have been reported only for the O-glucuronides.[69]

Enantioselective metabolism of the antiarrhythmic agent, drobuline (64) has been reported.[72] Three-fold higher plasma levels of the (-)-isomer than the (+)-isomer are observed when dogs are dosed with the racemate or with the individual enantiomers. More rapid metabolism of the (+)-isomer appears to account for the difference in plasma levels of the two enantiomers.

Chiral local anesthetic agents also demonstrate enantioselective disposition.[73] The less active R(-)-enantiomer of prilocaine (65) is prefer-



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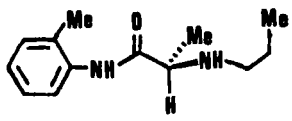
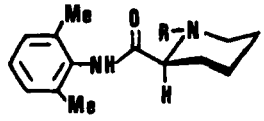


R(-)-65

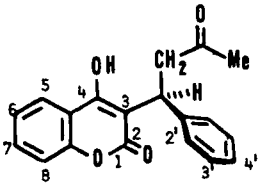


S(+)-66 R = Me

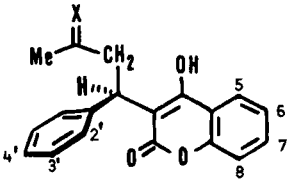
S(+)-67 R = n-C_4H_9

entially hydrolyzed and may be responsible for its greater methemoglobinemic toxicity. Absorption of the active S(+)-enantiomers of both mepivacaine (66) and bupivacaine (67) is more rapid that that observed for the more toxic R(-)-antipodes.

Intriguing species differences have been observed in the disposition of the oral anticoagulant, warfarin. In man,[74,75] the more active S(-)-warfarin (68A) is eliminated more rapidly than the R(+)-enantiomer 68B but the converse is true in the rat.[76] In humans, S(-)-warfarin is primarily 7-hydroxylated while the R(+)-isomer is reduced to the (R,S)-alcohol 69.[77,78] However, in rats, the S(-)-enantiomer is primarily 4-hydroxylated while the R(+)-isomer is 7-hydroxylated.[79-81] Kinetic[79-81] and spectral binding[82] studies with normal , phenobarbital, and 3-methylcholanthrene induced rat liver microsomes indicate that the observed differences in the oxidative metabolism of S(-)- and R(+)-warfarin are due to interactions with different forms of cytochrome P-450. Another oral anti-

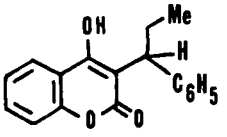


S[-]-68A



R[+]-68B X = O

(R,S)-69 X = N OH

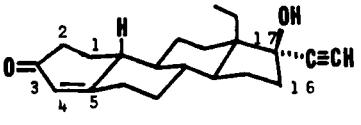


70

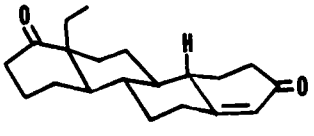
coagulant, phenprocoumon (70), also shows species variations in disposition of its enantiomers. The more potent S(-)-70 is less rapidly cleared from plasma than R(+)-70 in man[83] while the reverse holds in the rat.[84] These differences are related to enantioselective protein binding and tissue distribution.

Miscellaneous Drugs and Xenobiotics

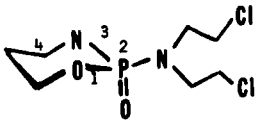
The two enantiomers of norgestrel follow different metabolic pathways. The biologically active (+)-enantiomer (71) has a longer half-life and yields metabolites resulting from enantioselective reduction (to 3α,5β-tetrahydronorgestrel) and 2α-hydroxylation. In contrast, the (-)-isomer undergoes preferential 16β-hydroxylation, A-ring aromatization to phenolic metabolites, oxidative rearrangement of the ethynyl group to the novel D-homoannulated metabolite 72 and other minor stereoselective biotrans-



[+]-71



72

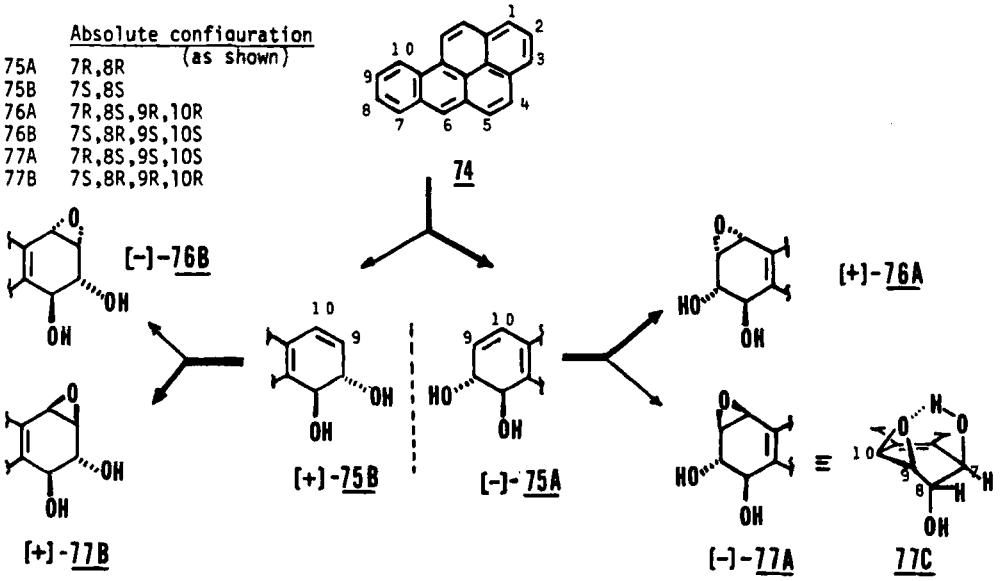


S[-]-73

formations.[85,86]

The chiral phosphorous atom in the antitumor agent, cyclophosphamide (73), gives rise to two enantiomers whose absolute configurations have been assigned recently.[87,88] The S(-)-enantiomer appears to be the more potent antitumor agent.[89] The preferential excretion of S(-)-73 in patients dosed with racemic drug suggests enantioselective metabolism of the R(+)-isomer.[89,90] It has been postulated that the improved antitumor activity of the (-)-isomer could reflect its less efficient detoxification by tumor tissues.[91,92] In mice, markedly more 4-ketocyclophosphamide and slightly less carboxyphosphamide are formed from R(+)-73 than from S(-)-73. The minor amount of unchanged cyclophosphamide detected is not enriched in either enantiomer.[91] In comparison, the individual stereoisomers of (±)-cis- and (±)-trans-4-methylcyclophosphamide reportedly display no marked differences in metabolism.[93]

The toxicity of the environmental carcinogen, benzo(a)pyrene (74) is believed to be mediated by metabolic conversion to reactive 7,8-diol-9,10-epoxide intermediates which covalently bind to crucial DNA and RNA.[94-97] Elegant studies have established the absolute stereochemistry of the diol epoxide intermediates.[98,99] Mammalian systems carry out these biotransformation with remarkable stereoselectivity.[99,100] For example, liver microsomes derived from 3-methylcholanthrene treated rats stereoselectively metabolize the prochiral benzo(a)pyrene principally to the (-)-trans-diol 75A which in turn undergoes stereoselective epoxidation to give a 9:1 ratio of the diastereomeric diol epoxides, (+)-76A and (-)-77A . On the other hand, the enantiomeric (+)-trans-diol 75B is epoxidized with even greater stereoselectivity to a 22:1 ratio of (+)-77B to (-)-76B. Results with normal or phenobarbital treated microsomes show qualitatively similar but less dramatic stereoselectivity in the epoxidation step.[99] This enantioselective difference in epoxidation is especially revelant in terms of the mutagenic and carcinogenic potential of the resulting diol



epoxides[101,102] (especially 77A and 77B in which the 9,10-epoxide may be more reactive towards nucleophilic attack as a result of anchimeric assistance by the neighboring cis C-7 hydroxyl group, see 77C [102]). Diol epoxide products formed from the (+)-75B diol are twice as mutagenic as those formed from (-)-75A.[99]

Other environmental pollutants such as insecticides also demonstrate enantiomeric differences in their metabolism. The (+)-enantiomer of O-methyl S-methyl 1-naphthyl phosphorothiolate is more rapidly O-demethylated than its (-)-isomer.[103] The prochiral O,O-dimethyl 1-naphthyl phosphorothionate shows remarkable stereoselective product formation yielding 90% of (-)-O-methyl 1-naphthyl phosphorothionate on O-demethylation. [103] Enantioselective hydration of chlordane-related cyclodiene epoxides to trans-diols[104,105] and enantioselective oxidation of (±)-cis- and (±)-trans-resmethrin[106] have been reported.

Differential disposition of R(+)- and S(-)-1-phenylethanol (formed from the metabolism of ethylbenzene) continues to be of interest.[8,107,108] The mechanism for the stereoselective conversion of ethylbenzene to S(-)-mandelic acid has also been reported.[108]

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