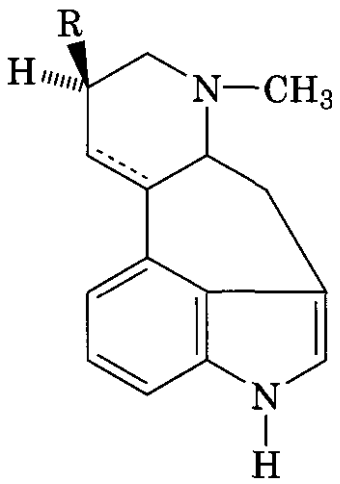
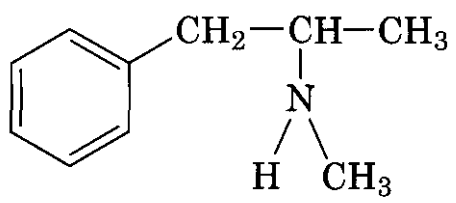


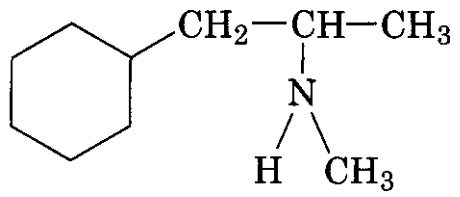
(85)

suggested (50) that the high affinity for the 5-HT, receptor exhibited by such compounds as (84) demonstrates that the C-5 hydroxyl group of serotonin can function as a hydrogen-bond acceptor at the receptor.

Replacement of the benzene ring of the potent indirect acting central noradrenergic stimulant methamphetamine (86) by a cyclohexane ring (compound 87) results in some



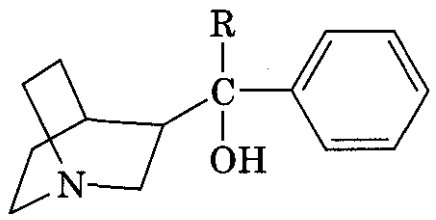
(86)



(87)

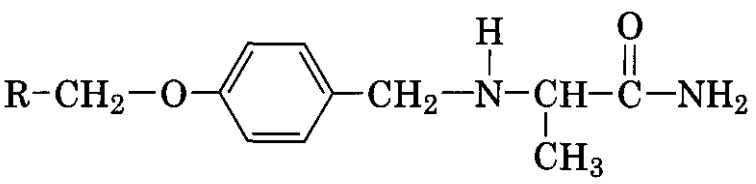
loss of pressor effect, but the drug, like amphetamine, has been used as a nasal decongestant, and it has CNS-mediated anorexigenic effect (52, 53). It is said to have somewhat less central stimulant action than the corresponding aromatic ring derivatives (54a-d).

The benzene (88) and cyclohexane (89) congeners have almost identical effects in blocking bronchoconstriction produced by histamine, serotonin, or acetylcholine in the guinea pig *in vivo* (55). They also showed identical LD_{50} values in mice. The stereochemistry of these compounds was not addressed.



(88) R = C_6H_5
(89) R = *c*-C_6H_{11}

In a study of anticonvulsant agents, the (*S*)-benzene ring analog (90) was somewhat more potent in a mouse assay than was the (*S*)-cyclohexane analog (91) (56). There was



(90) R = C_6H_5
(91) R = *c*-C_6H_{11}

only a slight difference in potency between (*R*)- and (*S*)-(90). The (*R*)-enantiomer of (91) was not reported.

5 ALTERATION OF STEREOCHEMISTRY AND DESIGN OF STEREOISOMERS AND GEOMETRIC ISOMERS

The earlier, almost universally accepted belief that if one enantiomer of a chiral molecule demonstrates pharmacological activity, the other enantiomer will be pharmacologically inert, is not valid. It must be anticipated that all stereoisomers of an organic molecule will exhibit pharmacological effects, frequently widely different and unpredictable. Many examples of qualitative and quantitative differences in metabolism of enantiomers are documented (57).

(±)-3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP, 92) was originally described (58) as having highly selective activity at dopaminergic autoreceptors.

At high doses (*R*)-(92) selectively stimulated presynaptic dopaminergic receptor sites, whereas at lower doses it selectively stimulated postsynaptic receptor sites (59). In contrast, the (*S*)-enantiomer stimulated presynaptic dopamine receptors and at the same dose level, it blocked postsynaptic dopamine recep-