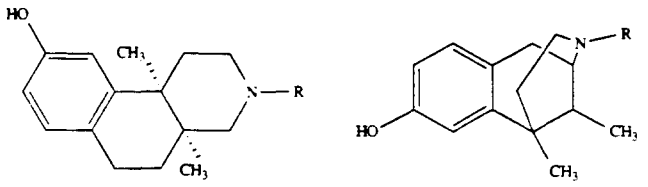
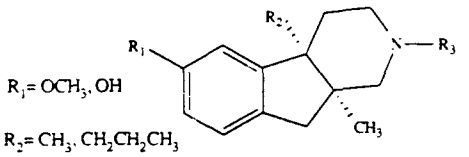
THE SEARCH FOR A PCP ANTAGONIST. THE DISCOVERY OF POTENT PCP-LIKE ACTIVITY IN A HEXAHYDROINDENO [2,1-c] PYRIDINE SERIES OF COMPOUNDS. Cantrell, B. E., L. G. Mendelsohn, D. D. Schoepp, J. D. Leander, R. B. Hermann and D. M. Zimmerman. Lilly Research Laboratories, A Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285.

Because phencyclidine (PCP) produces effects in man very similar to those in schizophrenia, it is felt that a PCP antagonist may have useful antipsychotic activity. The discovery of the PCP receptor and the subsequent development of reliable binding assays for this receptor, coupled with the ability to measure specific PCP-like behavioral effects, has made it practical to screen for PCP receptor antagonists.



BENZ [f] ISOQUINOLINES BENZOMORPHANS



HEXAHYDROINDENO [2, 1-c] PYRIDINES

Comparison of the known benzomorphans with the known benz[f]isoquinolines, led us to believe that the hexahydroindeno[2,1-c] pyridines above would have affinity for the PCP receptor. Accordingly, a series of these new compounds was synthesized. Their affinities for the PCP receptor were determined and compared with their ability to produce PCP-like catalepsy in pigeons. Compounds with potent PCP-like agonist activity were discovered. Maximum activity was obtained when R_1=hydroxyl, R_2=methyl and R_3=allyl. The potency of the compounds to produce PCP-like catalepsy correlated very well with their affinity for the PCP receptor, indicating that these compounds were full agonists at the PCP receptor.

SOLID STATE CONFORMATION OF PCP AND PCP ANALOGS. Carroll, F. I., G. A. Brine and K. G. Boldt. Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, NC 27709; and C. G. Moreland. Department of Chemistry, North Carolina State University at Raleigh, Raleigh, NC 27650.

Earlier reports from our laboratories as well as others describe the conformational properties of PCP and its analogs in solution. In addition, X-ray crystallographic studies of PCP and a few of its analogs have been reported. In this paper the solid state conformation of PCP and its analogs have been studied using CP/MAS ^{13}C high resolution nuclear magnetic resonance techniques. The resulting solid state conformational data is compared to X-ray data (when possible) and to conformational data derived from solution studies. Conformational similarities and differences between the solid state and solution structure are correlated with the biological activity.

MOLECULAR MECHANISMS IN PHENCYCLIDINE-INDUCED PSYCHOSIS AND ITS TREATMENT. Castellani, S. and S. J. Bupp. Department of Psychiatry, University of Kansas School of Medicine, Wichita, KS 67214.

Phencyclidine (PCP) produces a psychotic state in man with symptoms strongly resembling those in schizophrenia. Thus investigators have proposed that PCP-induced psychosis is a heuristic model of schizophrenia. Examination of molecular mechanisms mediating the behavioral and physiological effects of PCP may give an understanding of central mechanisms underlying PCP-induced psychosis and schizophrenia. Several central neurotransmitter/receptor actions of PCP may be involved in PCP-induced psychosis: enhanced dopaminergic neurotransmission, cholinergic inhibition, actions at PCP-*sigma* opiate receptors, and stimulation of serotonergic systems. This report examines each of these mechanisms with respect to mediation of PCP behaviors, interaction between different neurotransmitter systems, and hypothesized biochemical mechanisms and animal models of schizophrenia. Available data suggest that the psychotomimetic effects of PCP may be mediated by a combination of multiple PCP central actions; and in turn, the discovery of receptor mechanisms specific to PCP, i.e., the PCP-*sigma* opiate receptor and its putative endogenous ligand, has generated intriguing possibilities for future research into schizophrenia and related natural psychoses.

THE MULTIPLE BINDING SITES OF ^{3}H-PCP AND ^{3}H-TCP IN THE RAT AND THE HUMAN CNS. Chicheportiche, R., Y. Agid, I. Chaudieu, F. Finiels, J. Guiramand, F. Javoy-Agid, L. Journot, J.-M. Kamenka, A. Privat and J. Vignon. CNRS LP 8402-INSERM U249, Ecole Nationale Superieure de Chimie, Montpellier Cedex, France; CHU Pitie Salpetriere, 75634 Paris Cedex, France.

^{3}H-PCP has been extensively used to characterize the binding sites of PCP in CNS and other tissues. In a 50 mM Tris-HCl pH 7.7 buffer it has been shown that ^{3}H-PCP binds to a single class of sites with a Kd=0.25 μM and Bmax=2.4 pmol/mg protein on rat brain membranes. In the same conditions ^{3}H-TCP binding parameters are Kd=50 nM and a Bmax=1 pmol/mg protein. This difference in Bmax led us to investigate more precisely the binding sites of ^{3}H-TCP on rat