tory locomotor activity in mice at doses of 0.1 through 3.0 mg/kg IP, whereas higher doses caused less stimulation (10.0 mg/kg) or inhibited (30.0 mg/kg) exploratory locomotion. Numerous drugs of various classes were examined for their ability to selectively inhibit exploratory locomotion after a maximally stimulating dose (3.0 mg/kg) of PCP. None of the drugs which we examined consistently or selectively inhibited PCP-stimulated locomotor activity. That is, all drugs which reduced PCP-stimulated locomotion caused comparable percentage reductions of normal exploratory locomotion. However, because PCP alone had a biphasic dose-response, it was difficult to determine whether drugs which appeared to reduce PCP-stimulation had shifted the PCP dose-response curve to the left or to the right or simply reduced the maximum. Thus, when a drug appeared to reduce the locomotor stimulant effect of 3.0 mg/kg of PCP, it was always necessary to examine additional doses of PCP in the presence and absence of the second drug. Doses of PCP that maximally stimulated locomotor activity (e.g., 3.0 to 4.0 mg/kg IP) also caused mice to fall from a wire mesh platform when inverted 180 degrees, an effect which can be described as stimulated ataxia. We judged this procedure to be superior to locomotor activity measurement for examining anti-PCP effects, since the dose-response to PCP itself was monophasic. Again, none of the drugs which we tested appeared to antagonize this effect of PCP in mice. We conclude that none of the following drugs selectively block PCP-stimulated locomotion or ataxia in mice:

4-aminopyridine	diprenorphine	NMDA
d-amphetamine	haloperidol	phentolamine
apomorphine	ketamine	physostigmine
atropine	1-PIA	piracetam
baclofen	mephenesin	prazosin
bicuculline	meprobamate	propranolol
bromocriptine	metaphit	pyrilamine
chlorpromazine	methadone	quipazine
cimetidine	methysergide	reserpine
clonidine	morphine	rimcazole
clozapine	muscimol	THA
cyproheptadine	naloxone	yohimbine
diazepam	NECA	

INTRAVENOUS ANESTHETIC ACTIVITY OF BICYCLIC KETALS STRUCTURALLY RELATED TO KETAMINE AND ETOXADROL.

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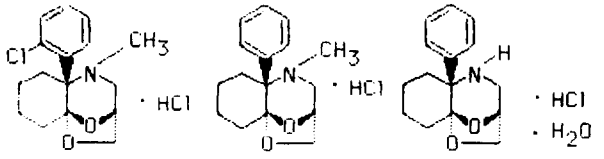
A limited series of bicyclic ketals bearing structural features common to the dissociative anesthetics ketamine HCl (K) and etoxadrol HCl (E) were prepared. The introduction of the ketal moiety of E into the K molecule provided the novel structural feature of this series.



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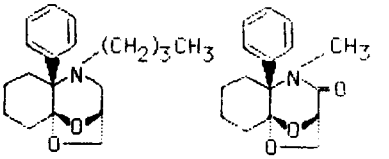

A 46682 A 46872

Screening for IV anesthetic activity was conducted in mice. Anesthetic ED50s for the reference compounds K, E and thiopental sodium (T) were 8.8, 15 and 20 mg/kg, respectively. The bicyclic ketal analog of K (A-46741) was inactive (ED50 > 50 mg/kg) but its deschloro derivative (A-46519) was anesthetic with an ED50 of 26 mg/kg, suggesting steric hindrance of the nitrogen. The importance of the secondary amine function present in both K and E was demonstrated with the N-desmethyl, deschloro ketal derivative A-47028 which had an ED50 of 8.5 mg/kg. Compounds A-46682 and A-46872 were inactive at a dose of 20 mg/kg. Acute LD50s of A-47028, K, E and T were 125, 82, 40 and 76 mg/kg, respectively, giving therapeutic indices of 14.7, 9.3, 2.7 and 3.8. The anesthetic activity of this bicyclic ketal series was confirmed in the rhesus monkey. Male rhesus monkeys, weighing 2.8–3.3 kg, were administered the test compounds by injection into the saphenous vein. The drugs were prepared as solutions in sterile water and were injected at a rate of 1 ml/min. Evaluation of anesthesia and related signs and symptoms was accomplished by the use of a twenty point check list adapted from Chen and Weston (Anesthesia and Analgesia **39:** 132, 1960). The monkeys were observed for onset and duration of and recovery from the anesthetic effects of K or the test drugs. Intravenous administration of two of the test compounds or K produced an immediate onset of anesthesia in rhesus monkeys. A-47028, at intravenous doses of 10.95 and 21.9 mg/kg, also produced anesthesia which was similar to that produced by K in equimolar doses of 10 and 20 mg/kg. The recovery times for A-47028 treated animals were longer than those of the K treated animals. A-46519, at intravenous doses of 10.8 and 21.6 mg/kg, produced anesthesia which was about equal to K (10 and 20 mg/kg) in duration and time to full recovery. A-46741 (12 and 24 mg/kg) produced no anesthesia when administered intravenously in rhesus monkeys.

PHARMACOLOGICAL STUDIES SUGGEST THAT *SIGMA* RECEPTORS LABELED *IN VIVO* WITH [^{3}H]-(+)-SKF10047 ARE PREDOMINATELY OF THE HIGH AFFINITY TYPE.

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The *sigma* receptor, so named because of the distinct pharmacological profile produced by its prototypic agonist SKF-10047 (N-allylnormetazocine), is believed to mediate mania and other psychotomimetic effects in man. While this *sigma* receptor has received extensive characterization *in vitro*, little information is available on the nature of the *sigma* site *in vivo*. It is possible to label dopaminergic, opiate, cholinergic, serotonergic and benzodiazepine receptors *in vivo* after IV administration of appropriately labeled ligands. In the present study, we describe the *in vivo* labeling of