Table I—Head Twitch Responses in Mice Produced by Phenethylamine Derivatives

Compound	ED_{50} (95% Limits), mg/kg ip[a]	Onset, min	Duration, min
(±)-2-Hydroxy-4,5-dimethoxyphenethanolamine (I)	17 (12.1–23.8)	2–18	2–24
(±)-2-Hydroxy-4,5-methylenedioxyphenethanolamine (II)	56 (25.4–123.2)	2–6	2–22
Mescaline	5.3 (3.6–7.3)	2–14	2–28

[a] The ED_{50} values reported are calculated for the free base concentrations of the test compounds.

derivatives I and II were about one-third and one-tenth as active as mescaline, respectively. From these results it appears that I could be an endogenous psychotogen responsible for schizophrenic manifestations as postulated by Shulgin *et al.* (4).

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Chemical Constituents of Gentianaceae XI: Antipsychotic Activity of Gentianine

Keyphrases □ Gentianine—antipsychotic activity evaluated □ Gentianaceae—chemical constituents, antipsychotic activity of gentianine evaluated □ Antipsychotic activity—gentianine screened, chemical constituents of Gentianaceae

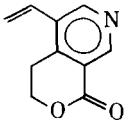
To the Editor:

In an attempt to locate the active principle(s) of *Swertia chirata* (1), we examined the psychopharmacological profile of its major alkaloid, gentianine (I). The first report (2) on the central nervous system (CNS) activity of this compound was limited to the observation that "in weak doses it appears to stimulate the central nervous system, but in larger amounts it shows a paralyzing action." Preliminary pharmacological screening of the alkaloid, however, reflected its CNS depressant activity even in small doses (3). The results obtained in the present investigation point to a persuasive explanation of this activity and prompt us to report the antipsychotic profile of action of this compound.

Pharmacological studies were conducted on albino mice[1] (18–25 g) and albino rats[1] (80–120 g). The animals were fed on standard pellet diet[2]. All experiments were conducted at ambient temperature of 28 ± 2°. Unless stated otherwise, gentianine was used in a dose of 20 mg/kg ip and pretreatment time was 1 hr. At least 10 animals were used for drug-treated and control groups, the latter receiving only the vehicle, distilled water.

In primary observational tests (4), gentianine, in small doses (10–20 mg/kg ip), markedly diminished spontaneous motility and produced sedation and ptosis in albino mice and rats, but reflexes were intact and the animals responded to external stimuli. On increasing the dose (50–100 mg/kg), hind-limb paralysis and catalepsy were produced. The cataleptic animals remained stationary when placed on a vertical wire netting and maintained the awkward posture when one hind limb was placed on a cork. However, they responded to painful stimuli and retained the righting reflex. Gentianine produced hypothermia in albino rats as recorded by a rectal thermister probe. Since these observations are indicative of antipsychotic activity, gentianine was subjected to further pharmacological screening as follows.

The effects of gentianine on hexobarbital hypnosis, amphetamine toxicity and stereotypy, and lysergide-induced symptoms were evaluated. Gentianine sig-



I

[1] B. N. Ghosh & Co, Calcutta, India.
[2] Hindusthan Levers, Calcutta, India.

nificantly potentiated (80%) hexobarbital (100 mg/kg ip) sleeping time in albino mice (5); it markedly diminished (88%) amphetamine (20 mg/kg ip) toxicity in aggregated mice (6) and antagonized amphetamine- (10 mg/kg sc) induced stereotypy (continuous sniffing, biting, and compulsive gnawing) in albino rats (7). The alkaloid completely inhibited lysergide- (3 mg/kg sc) induced piloerection and tremors in mice (8).

Using rats and mice, the effects on the rotarod test, conditioned avoidance response, and induced aggressive behavior were examined. Gentianine markedly inhibited (80%) the ability of trained mice to remain on a rotating rod for a maximum time trial of 180 sec (9). The alkaloid selectively blocked the avoidance response to the conditioned stimulus (buzzer), without affecting the escape response to the unconditioned stimulus (electric shock), when tested on trained rats (10). However, in higher doses (50 mg/kg ip), there appeared to be an appreciable motor deficit as characterized by suppresssion of the escape response (40%) to the unconditioned stimulus in these animals. Gentianine inhibited (60%) foot-shock-induced fighting behavior in paired mice (11).

The effects of gentianine on morphine analgesia, anticonvulsant action of diphenylhydantoin, electroshock seizure, and pentylenetetrazol convulsion were also determined. Gentianine markedly potentiated (150%) the analgesic activity (12) of subanalgesic doses (2 mg/kg ip) of morphine (13) but had no analgesic activity *per se* at this dose (20 mg/kg). It significantly potentiated (60%) the anticonvulsant activity of a subanticonvulsant dose (2.5 mg/kg ip) of diphenylhydantoin but had no anticonvulsant activity *per se*. With higher doses (50 mg/kg ip), however, it showed noteworthy anticonvulsant activity (40%) as tested by the electroshock seizure method (14). In higher doses (50–100 mg/kg ip), gentianine offered significant protection (70%) against pentylenetetrazol- (70 mg/kg sc) induced convulsion (15).

The toxicity (16) and the LD_{50} of gentianine after intraperitoneal administration in albino rats were studied; the LD_{50} was calculated as 276 mg/kg. The drug appears to possess only a moderate to low order of toxicity as evidenced from the lack of any obvious toxicity on prolonged intraperitoneal administration, 20 mg/kg daily for 3 weeks.

Gentianine exhibited significant antipsychotic activity in the battery of tests accepted for arriving at such a conclusion (17). It has the added advantage of its minimal toxicity. The alkaloid, bearing a skeleton (lactonic monoterpene) different from those of known antipsychotic agents, is thus of potential importance as an antipsychotic drug.

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Renal Contribution to Drug Biotransformation

Keyphrases □ Renal metabolism—contribution to drug biotransformation, true renal clearance values □ Drug biotransformation—renal contribution, assessment of determination of true renal clearance values □ Metabolism, drug—renal contribution to drug biotransformation, assessment of determination of true renal clearance values

To the Editor:

Wan and coworkers (1–4) recently described an imaginative pharmacokinetic approach for assessing the contribution of the kidneys to the biotransforma-