Introduction - During the last year there has been a proliferation of reports of compounds possessing depressant activity. Some of the compounds will be considered in other chapters, but because of reports of sedative-hypnotic and anticonvulsant activity in certain compounds, they may also be covered in this section. This is especially true in the case of the benzodiazepines where it is difficult to separate antianxiety from sedative-hypnotic activity. An attempt was made to cover those compounds where more than preliminary screening data is available or where novel structural types of compounds were presented.

Sedatives and Hypnotics - Insomnia is among the most common disorders dealt with in medical practice and despite much research work in recent years, sleep and insomnia are not well understood. The causes of insomnia and its management have recently been reviewed by Johns.\(^1\) In his review, he describes both the intrinsic and extrinsic factors which can cause insomnia and the practical aspects of its treatment.

In an effort to better understand sleep and the effects of hypnotic drugs on sleep patterns, numerous studies have been undertaken to evaluate the effect of drugs on polygraphically monitored sleep in man. These studies have been evaluated critically by Freem\(\text{on}\)\(^2\). He describes the way that sleep laboratory studies are done, the division of sleep into its various stages, and the numerous pitfalls in this kind of research. The review by Freem\(\text{on}\) includes a summary of the results obtained in 65 different studies with both new experimental compounds and currently available hypnotic and central nervous system drugs.

The clinical choice of sedative-hypnotic drugs for the management of insomnia has also been reviewed recently by Greenblatt and Shader.\(^3\) The authors review the clinical conditions in which hypnotics should be used as well as the advantages and disadvantages of currently available hypnotic agents. They conclude that current evidence favors benzodiazepine derivatives since suicide is virtually impossible with them and they do not interact with oral anticoagulants.

A characteristic of most benzodiazepines is their propensity to produce sedation and hypnosis in both animals and man. Numerous papers have appeared in the last year describing the hypnotic activity of flurazepam (I) in man.\(^4\),\(^5\),\(^6\) The effect of various hypnotics on performance (vigilance, eye-hand coordination, cognitive-association and decision making) was reported by Bixler et al\(^6\) who found that in general secobarbital produced a more consistent and greater decrement in performance than flurazepam.
Sleep laboratory studies on lorazepam (WY 4036, II) have shown that this compound depresses REM sleep but there is no rebound increase in REM during the post-drug nights. Stage 4 sleep was not decreased by lorazepam. No changes were seen in clinical laboratory studies or physical examinations.

The potent activity of the triazolobenzodiazepines (U-31,889, III and U-33,030, IV) has been summarized. The effect of one of these derivatives, compound (III) in sleep laboratory studies has been reported by Itil et al who conclude that compound III could be useful in chronic sleep disturbances and in patients with nightmares, somnambulism and night terrors.

Compound V (S-1530), the 1-methyl derivative of nitrazepam, a marketed hypnotic agent, has been shown to have both antianxiety and hypnotic activity clinically. In animals compound V was found to be more potent than either nitrazepam or diazepam as a muscle relaxant, anticonvulsant and "sleep inducer".

Compound VI (CS-370) was found in the process of screening derivatives of the benzodiazepine derivative, oxazolam. This compound is more potent than oxazolam in laboratory tests and has a lower toxicity than does diazepam.

The animal pharmacology of perlazine (VII) has recently been reviewed and the compound has been postulated to differ in mechanism of action from other sleep promoting agents. Moreover, the compound
differs pharmacologically from potent neuroleptics and also from the benzodiazepines.

In sleep laboratory studies in man, compound VII caused a reduction in REM sleep but did not reduce stage 3 or 4 sleep. This was interpreted as advantageous since stage 3 and 4 sleep can be linked to the restorative properties of sleep.

The 2-monofluoromethyl analog of methaqualone (VIII - HQ-355) has been reported to be a more potent hypnotic agent than methaqualone with a lower toxicity. Compound VIII also possessed more potent anticonvulsant activity.

K. Nagarajan et al have reported the CNS depressant activity of a series of derivatives of benzodiazepinones. One of the derivatives, compound IX, showed dose related sedation, ptosis and ataxia. The compounds had low toxicity.

The methylimidazole derivatives (X, XI) resemble general anesthetics, as doses causing loss of righting reflex lie close to those affecting loss of other reflexes. At non-hypnotic doses, the compounds (X, XI) potentiated the hypnotic effect of sodium phenobarbital.
Two oxazolinone derivatives (XII, XIII) were found to exhibit sedation and muscle relaxation. Compound XII was also found to potentiate the hypnotic effect of alcohol. This was surprising for this series of compounds because most other derivatives antagonized barbiturate-induced sleep.

The most interesting series of compounds possessing CNS depressant activity are the bicyclononanol derivatives. Compound XIV, the most active of the series, is equivalent in activity to chlordiazepoxide on all endpoints except antagonism of pentylenetetrazol-induced clonic convulsions. The compound is also much less toxic than chlordiazepoxide.

Finally, pharmacological studies with a new indole alkaloid, rugulovasine (XV), have shown that the alkaloid depressed spontaneous motor activity, prolonged the duration of loss of righting reflex caused by barbiturate, and enhanced the similar potentiating effect of reserpine in mice.

**Anticonvulsants** - Although primidone has been in clinical use since 1952, little work has been done on its metabolism in man. Baumel et al found that after a single oral dose of primidone in man, PEMA (phenylethylmalonamide) appeared in the serum, whereas phenobarbital was not detected. This finding differs from previous studies in animals where administration of primidone results in the production of PEMA as well as phenobarbital. In epileptic subjects receiving primidone chronically, however, both PEMA and phenobarbital accumulated in the serum. PEMA was found to have anticonvulsant activity in rats and also potentiated the anticonvulsant activity of phenobarbital. These results correlate with the recent evidence from animal studies that the total anticonvulsant action of primidone exceeds that attributable to phenobarbital alone.

One of the properties of many central nervous system depressant drugs is their ability to antagonize seizures produced by convulsant agents or electroshock. The benzodiazepine derivatives are especially active in this regard with pronounced activity against chemically induced
seizures in animals but with less activity against electroshock seizures.

The 1-allylcarbamoyl benzodiazepine (XVI) is equipotent to diazepam in antagonizing convulsions induced by nicotine, thiosemicarbazide, strychnine and pentylentetrazol and electroshock. The ED50 value to antagonize the chemically induced convulsions is significantly lower than that required to antagonize maximal electroshock-induced seizures.

The 2,6-difluorobenzodiazepinone (XVII) also possesses potent anticonvulsant activity against chemically induced convulsions. It is approximately four to ten times as active as diazepam in this regard. The monofluoro derivative (XVIII) is at least as active as the difluoro derivative (XVII) as an anticonvulsant.

The pharmacological properties of prazepam (XIX) have previously been published, however, a more extensive study by Boissier et al shows that the compound has potent anticonvulsant activity with low sedative action, a wide margin of safety, and a long duration of activity.

A thienodiazepine derivative (XX) is two to three times more active than diazepam and six to nine times more active than chlordiazepoxide in antagonizing pentylentetrazol and bemegride induced convulsions in mice. The compound has been tested clinically in preoperative sleep disturbances and found to be very effective.
2-Cyclohexylamino-1-phenylethanol (XXI) has been found to potentiate the hypnotic effect of pentobarbital and to markedly antagonize convulsions produced by pentylenetetrazol but not electroshock or strychnine.\textsuperscript{27} Cyclic compounds (XXII) derived from XXI showed less activity under the same test conditions.

![Chemical structures](image)

The stereo structure-activity relationships of a series of acetyl-\textsuperscript{D(R)} and \textsuperscript{L(S)}-N- succinimides (XXIII, XXIV) and glutarimides (XXV, XXVI, XXVII) were studied.\textsuperscript{28} Succinimides and glutarimides having the \textsuperscript{D(R)} configuration exhibit activity equal to or greater than the activity exhibited with the \textsuperscript{L(S)} anticonvulsants. Compounds XXIII, XXIV, XXV, XXVI and XXVII have activity which compares favorably with the activity of drugs of clinical significance.
Fernández-Tomé et al. have reported on the synthesis of a series of 2,5 dihydro-1,2,4 benzothiadiazepine 1,1-dioxides of which compound XXVIII is representative. Compound XXVIII antagonizes maximal electroshock seizures in mice but has weaker activity against pentylentetrazole and strychnine induced convulsions. The toxicity of this compound is extremely low (LD50 > 2000 mg/kg, i.p.).

Compound XXIX produces the same degree of CNS depression as phenobarbital or chlordiazepoxide and possesses anticonvulsant activity against maximal electroshock induced convulsions.

**General Anesthetics** - The pharmacological properties of CT 1341 (Althesin), a steroidal anesthetic agent which contains alphaxalone and alphalolone acetate, have recently been described. It is a potent intravenous anesthetic in animals which produces rapid induction of anesthesia without vascular irritation. Initial trials of CT 1341 in man appear to substantiate the finding in animals. In further anesthetic, cardiovascular and respiratory studies in animals, it was found that CT 1341 has a wider therapeutic latitude, produces less respiratory depression, and has greater efficacy than currently used intravenous anesthetics.

Thirty-four halogenated methyl ethyl ethers were evaluated as volatile general anesthetics by Terrell et al. Twelve of the compounds had good anesthetic properties in mice. Compounds XXX and XXXI are currently undergoing clinical trial.

\[
\text{F}_2\text{HCOCCHClCF}_3 \quad \text{F}_2\text{HCOCF}_2\text{CHClF}
\]

XXX

XXXI

An additional series of methyl pentahaloethyl and methyl heptahalopropyl ethers were evaluated as anesthetic agents. Both sedation and anesthesia were observed but the potency in general was diminished when compared to the halogenated methyl ethyl ethers.

**REFERENCES**

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