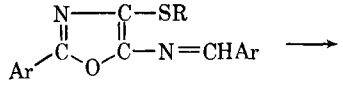
Somnifacient Action of α-Methylmercaptohippuramide

By ARNOLD R. MARTIN*, F. H. MEYERS, and ROGER KETCHAM

α-Methylmercaptohippuramide has an LD_{50} in mice of 670 ± 20 mg./Kg. Sublethal doses produce sleep but not anesthesia. In preliminary tests on a dog, the drug showed no effect on the autonomic system, nor did it alter the normal responses to the autonomic drugs or histamine. Its pharmacology appears to be similar to that of trimeglamide and thalidomide to which it is structurally related.

DURING THE COURSE of chemical studies on the oxazole condensation products (I) from *S,S'*-dialkyl or diaryl dithioöxaldiimidates and aromatic aldehydes (1), it was found that these oxazole derivatives are rapidly hydrolyzed by acids to open chain nitriles (II), or, under only slightly more vigorous conditions, to the corresponding amides (III).



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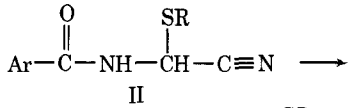

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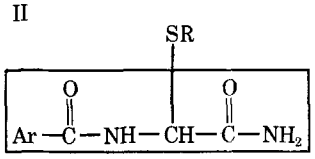
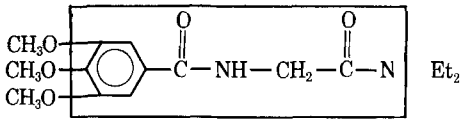
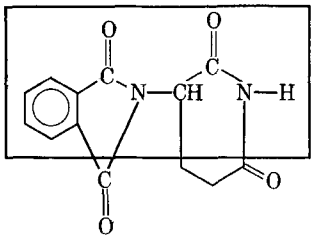


IIIa, R = CH_3, Ar = C_6H_5



IV



V

Scheme I

The structural similarity of these amides (III) to trimeglamide (IV) and thalidomide (V), which is pointed out in Scheme I, suggested that these sulfur-containing hippuramides might possess similar biological properties. Compound IIIa was therefore subjected to preliminary pharmacological testing.

EXPERIMENTAL

Experiments with Mice—Male Swiss albino mice, weighing 19–23 Gm., were injected (i.p.) with a suspension containing 25 mg./ml. of IIIa in 20% glycerin in water with 0.1% polysorbate 80[1] as a suspending agent. Ten mice at each dose level were treated in a group and observed periodically in a well-lighted room. The data (Table I) give an LD_{50} of 670 ± 20 mg./Kg. (2).

At doses below the LD_{50}, the compound caused the mice to show increased spontaneous activity, to become sluggish and depressed, and to fall asleep if left alone. The mice were easily aroused by external stimuli and behaved normally during the period of stimulation. Neither ataxia nor excitement was observed. The induction period was 15 to 45 min.; the duration of action was 2 to 6 hr.

The gross effects of thalidomide, compound IIIa, trimeglamide, and the thiazolothiazole mentioned below were compared following intraperitoneal injection into dogs, rats, mice, and guinea pigs. The effect, induction of normal sleep in the undisturbed animal, was the same for each drug in each species, including the guinea pig.

Mice given doses near and above the LD_{50} exhibited the same general symptoms mentioned above. However, all of the mice which died passed from a depressed to a convulsive state. Marked ataxia and disorientation were observed at these doses. The convulsions did not appear asphyxial, although some depression of respiration was noted. Several mice survived the convulsions which lasted for about 10–20 min.

Three mice, each given 750 mg./Kg. of IIIa and kept in separate cages in a semidarkened environment, exhibited qualitatively the same symptoms as mice given subtoxic doses, *i.e.*, they moved to a darkened corner of the cage and slept. All of these mice survived and none exhibited convulsions. Thus an LD_{50} determined by keeping the treated mice in separate cages would probably be higher than the group LD_{50}.

Anesthetized Dog Experiment—A dog was anesthetized with sodium pentobarbital, 30 mg./Kg. i.v. Carotid blood pressure was measured with a pressure transducer and respiration with a pneumotachygraph in the airway. These functions and the electrocardiogram were recorded on a polygraph. The effects of intravenous injections into the femoral vein of 10 mcg./Kg. of epinephrine, methacholine, and histamine, and the response to vagal stimulation

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The authors wish to dedicate this paper to Dean T. C. Daniels, whose leadership at the University of California has done so much to raise the standards of education and research in the pharmaceutical sciences.

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[1] Marketed as Tween 80 by Atlas Chemical Industries, Inc., Wilmington, Del.

TABLE I—ACUTE TOXICITY DATA ON MICE

Dose, mg./Kg.	Mortality
500	0/10
600	1/10
650	5/10
700	6/10
750	8/10

LD_{50} 670 ± 20 mg./Kg.

were determined during a control period and for 6 hr. after the injection of III*a*. The i.v. injection of 2 mg./Kg. and 8 mg./Kg. did not alter the arterial pressure or electrocardiogram or the response to vagal stimulation or challenge injection of the amines. The slight respiratory depression seen was equal to that produced by the suspending agent alone. Similarly, no changes were seen after the i.m. administration of 40 mg./Kg. of III*a*. These results suggest an absence of autonomic and antihistamine effects.

DISCUSSION

The pattern of effects suggests that this compound is not a sedative-hypnotic since it does not produce anesthesia even in large doses. Nor does it have behavioral or autonomic effects suggestive of a tranquilizer of the phenothiazine type. It appears to be similar in its action to thalidomide and trimeglamide to which it is chemically related and to the chemically unrelated 2,5-bis(1,1-dimethyl-3-cyanopropyl)thiazolothiazole (3).

The specific and tragic toxic effect of thalidomide need not obscure the fact that thalidomide defines a purely somnifacient class of drugs potentially safer than the barbiturates. The experience referred to in this paper suggests that drugs of this new class can be recognized during a routine screening and that the action may reside in structures chemically distant from thalidomide.

REFERENCES

(1) Martin, A. R., and Ketcham, R., *J. Org. Chem.*, **31**, 3612(1966).
(2) Litchfield, J. T., and Wilcoxon, F., *J. Pharmacol. Exptl. Therap.*, **96**, 99(1949).
(3) Fikrat, H. T., and Oneto, J. F., *J. Pharm. Sci.*, **51**, 527(1962).

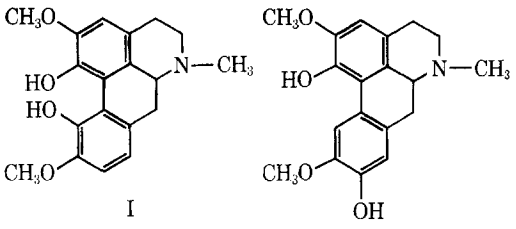
Opium Alkaloids IV. Isolation of Isoboldine

By EINAR BROCHMANN-HANSSEN, BENDIK NIELSEN, and KENTARO HIRAI

The aporphine alkaloid isoboldine has been isolated from opium. It has been identified by NMR and mass spectrometry and by comparison of its infrared spectrum with that of synthetic (±)-isoboldine. ORD measurements have shown that the isolated alkaloid has the absolute configuration corresponding to the (*S*)-series. Possible biosynthetic pathways for isoboldine are discussed briefly.

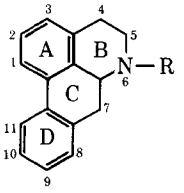
THE APORPHINE alkaloids are widely distributed in nature and, although they occur abundantly in the *Papaveraceae* family, it is only recently that alkaloids of this type have been found in opium. In 1965 Nijland (1) reported the isolation of corytuberine (I) and magnoflorine (*N*-methylcorytuberine). A third member of the aporphine group has now been obtained from opium and identified as isoboldine (II). This alkaloid has previously been isolated from *Nandina domestica* by Tomita *et al.* (2, 3).

All naturally occuring aporphine alkaloids which are known so far are substituted in positions 1 and 2 (III). The amine nitrogen may be secondary, tertiary, or quaternary, and ring D is either unsubstituted or has one or more oxygen functions in positions 8, 9, 10, and 11.



I

II



III

EXPERIMENTAL

Isolation—Dried and powdered opium of Indian origin (1,755 Gm.) was first extracted with petroleum ether, b.p. 40–60°, in a Soxhlet extractor. After drying in air, the opium powder was moistened with an aqueous solution of sodium carbonate (185 Gm. anhydrous Na_2CO_3 in 750 ml. H_2O) and dried

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Previous paper: Brochmann-Hanssen, E., and Nielsen, B., *J. Pharm. Sci.*, **55**, 743(1966).