A NEW POTENT ANALOGUE OF NISENTIL

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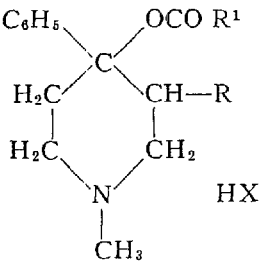
PREVIOUS work has shown that the diastereomeric 1,3-dimethyl-4-phenyl-4-propionoxypiperidines have powerful analgetic activity in experimental animals (1). The α-diastereomer, Ro 2-1196 (= alphaprodine hydrochloride = Nisentil ®HCl), is less active (about equal to morphine in rats) but better tolerated than the β-diastereomer, Ro 2-1779, and was introduced commercially as a short-acting analgetic (2,3,4).

TABLE I

1-METHYL-3-SUBSTITUTED-4-PHENYL-4-ACYLOXYPIPERIDINES



Compound Ro 2-	R	R1	HX	M P (corrected)	AD50 (Intravenously in mice, mg /kg)	LD50
1196	methyl (α)†	propionoxy	hydrochloride	220–221	0 80	51 0
1779	methyl (β)†	propionoxy	hydrochloride	200–201	0 30	54 8
1932	ethyl* †	propionoxy	hydrochloride	230	0 74	45 0
7113	allyl (α)	propionoxy	hydrochloride	185–186	0 07	45 7
7839	allyl (β)	propionoxy	hydrochloride	202–203	0 26	53 0
7825	allyl (α)	butyroxy	hydrochloride	151–152	0 25	37 5
7826	allyl (α)	acetoxy	hydrochloride	211–212	0 45	67 5
7176	n-propyl (α)	propionoxy	hydrochloride	203–205	2 25	48 0
7142	dibromoallyl (α)	propionoxy	hydrochloride	182–183	1 36	53 0
7471	crotyl (α)	propionoxy	d-tartrate	95–97	28 40	57 5
7483	crotyl (β)	propionoxy	maleate	126–130	21 50	53 5
7482	n-butyl*	propionoxy	d-tartrate	140–143	20 00	41 5
7516	n-hexyl*	propionoxy	dl-malate	98–100	20 00	27 5
7994/1	benzyl*	propionoxy	hydrochloride**	207–208	24 0	39 0

*Relative configuration unknown—probably (α)

**Tested as dl-malate (water soluble, non-crystalline)

†Other pharmacological results published in (1)

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With the hope of obtaining compounds with qualitative and quantitative differences in analgetic potency, the structure was modified to obtain the 1-methyl-3-substituted-4-phenyl-4-acyloxy-piperidines described in Table I, which also presents the values of analgetic activity (AD_{50}) and toxicity (LD_{50}) of the compounds when administered intravenously to mice. Analgesia was assessed by mechanical compression of the tail. All compounds were tested in the form of racemates.

One of these agents, viz, Ro 2-7113 (1-methyl-3-allyl-4-phenyl-4-propionoxy-piperidine hydrochloride), while of the same order of toxicity as Ro 2-1196, was found to be considerably more active. The favourably high ratio between the 50 per cent lethal and analgetic doses is evident from Table II. In rats, Ro 2-7113

TABLE II

ANALGETIC ACTIVITY AND TOXICITY OF RO 2-7113 AND RO 2-1196 IN MICE, RATS AND RABBITS

Animal	Route	Compound RO 2-	AD_{50}* mg /kg	LD_{50} mg /kg.	Ratio LD_{50}/AD_{50}
Mice	I V.	7113	0 07	46 0	653 0
	I V.	1196	0 80	51 0	63 8
Rats	I V	7113	0 05	13 4	268 0
	I V	1196	0 62	25 0	40 3
	S C	7113	0 13	80 0	615 4
	S C.	1196	1 00	50 0	50 0
	P O	7113	12 0	125 0	10 4
	P O	1196	21 0	90 0	4 3
Rabbits	I V.	7113	06	7 8	130 0
	I V	1196	2 0	22 0	11 0

*Calculated in mice and estimated for rats and rabbits For latter species, doses represent those required to prolong reaction time 100 per cent

exhibited a high order of analgetic activity when measured by a modification of the Ercoli and Lewis technique (5). The ratio between toxicity and analgesia was greater than that of Ro 2-1196 when the drugs were given intravenously, subcutaneously or orally. In rabbits, comparable results were obtained by the intravenous route of administration, although equivalent degrees of analgesia were associated with similar degrees of respiratory depression when studied by combining the Ercoli and Lewis technique for measurement of analgesia and the Wright technique (6) for measuring minute volume exchange. Significant analgetic effects were also demonstrated in the dog.

Clinical trials with Ro 2-7113 were carried out on a limited scale by the oral and intravenous routes. Thirteen ambulatory patients with inoperable malignancies received alternately 2 to 6 mg. Ro 2-7113 or levorphan. The drugs were administered orally, 4 to 8 hours apart, for periods ranging from 4 to 97 days. The onset, duration, and degree of analgesia and the incidence and severity of

side effects were recorded following the use of both compounds. A comparative analysis of results could not be made because of the progressive nature of the underlying pathology. However, the impression was gained that the onset, degree, and duration of action of identical oral doses of Ro 2-7113 and levorphan were quite similar. The incidence of side effects such as drowsiness, vertigo, and nausea was usually lower and the severity less marked after the administration of Ro 2-7113 than after levorphan. Administered intravenously on a weight basis, Ro 2-7113 was found to be 2 to 3 times, 10 times, and 25 to 30 times more potent than morphine, alphaprodine, and meperidine, respectively. By this route, the duration of action of Ro 2-7113 and alphaprodine was approximately equal. As with other potent narcotic analgetics, large doses of Ro 2-7113 produced marked respiratory depression which was readily antagonized by levallorphan.

Ro 2-7113, in combination with levallorphan, was used intravenously for supplementation of N_2O–O_2 anaesthesia in 230 patients. The initial dose of Ro 2-7113 was 0.1 mg /kg. and that of the narcotic antagonist, 0.02 mg /kg. The anaesthetic management (7) was the same as that used for 852 patients who received 1 mg /kg. of alphaprodine and 0.02 mg /kg of levallorphan as initial doses. In these two series, the effects of Ro 2-7113 and of alphaprodine were identical for all practical purposes

The preliminary observations here reported suggest that Ro 2-7113 may become a clinically useful analgetic.

REFERENCES

1 RANDALL, L O & LEHMAN, G J Pharmacol 93 314 (1948)
2. HAPKE, F B & BARNES, A C Amer J Obstet Gynec 58 799 (1949)
3 SMITH, E J & NAGYFY, S F Amer J Obstet Gynec 58 695 (1949)
4 THELEN, C Jackson Clin Bull *11* 170 (1949)
5 ERCOLI, N & LEWIS, M. N J Pharmacol *84* 301 (1945)
6 WRIGHT, C I J Pharmacol *51* 327 (1934)
7 FOLDES, F F, LIPSCHITZ E, WEBER, G M, SWERDLOW, M, & PIRK, L A J A M A *160* 168 (January, 1956)