servations that 11-hydroxy aporphine is a weaker dopamine-like agent than is apomorphine (Granchelli, Neumeyer & others, 1971) and that 10-hydroxy-11-methoxyaporphine and 11-hydroxy-10-methoxyaporphine have little dopamine-like activity (Cannon, Smith & others, 1972).

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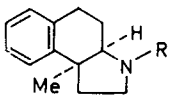
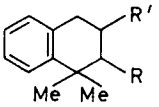
The synthesis and analgesic and cns-suppressant activities of 2-amino-, 2-methylamino-, and 2-dimethylamino-1,1-dimethyltetralin hydrochlorides

Recently a series of 3-amino-1,1-dimethyltetralins (Martin, Parulkar & others, 1969) and three compounds having structures (I, R=H, Me and CH_2—CH=CMe_2) (Harper & Raines, 1969) have been synthesized as potential analgesic agents. Although analgesic evaluation of the latter three compounds was not reported [subsequent to the completion of this present work, it has been brought to our attention by Dr. D. C. Bishop that these compounds do not possess analgesic activity], 1,1-dimethyl-3-dimethylaminotetralin (II, R = H, R′ = NMe_2) possessed an analgesic activity 2·5 times that of codeine (Martin & others, 1969). In view of this, and since compounds of type I possess a 2-aminotetralin moiety with a quarternary carbon atom at position 1, we have synthesized and pharmacologically evaluated the title compounds.



I



II

1,1-Dimethyl-2-tetralone, prepared from 2-tetralone (Soffer, Bellis & others, 1963) using two successive 1-methylations (Stork, Brizzolara & others, 1963; Harper & Raines, 1969) was converted into the oxime, colourless prisms from ethanol, m.p. 99–100°, by reaction with hydroxylamine hydrochloride in the presence of dry pyridine. Upon reduction with lithium aluminium hydride in ethereal solution the oxime afforded 2-amino-1,1-dimethyltetralin (II, R=NH_2, R′=H), a yellow oil. This was *N*-formylated by reaction with methyl formate at 100° for 24 h and the product (II, R=NH—CHO, R′=H) was reduced with lithium aluminium hydride in ethereal solution to give 1,1-dimethyl-2-methylaminotetralin (II, R=NHMe, R′=H), a brown oil. This monomethylamino derivative was also prepared directly from 1,1-dimethyl-2-tetralone by reaction with *N*-methylformamide in the presence of formic acid (for an analogous reaction with 3-tetralones see Martin & others, 1969). *N*-Methylation with formaldehyde-formic acid (Clark, Gillespie & others, 1933)

Table 1. *Relative pharmacological effects of 2-amino-, 2-methylamino- and 2-dimethylamino-1,1-dimethyltetralin hydrochlorides.*

Dose (mg/kg)	Route		Compound II, R′=H, R= $\overset{+}{N}H_3Cl^-$	$\overset{+}{N}H_2MeCl^-$	$\overset{+}{N}HMe_2Cl^-$
100	Oral	1. Effects of behaviour in the mouse	±a	±b	±c
100	Oral	2. Effects on body temperature	++d	±e	±f
100	Oral	3. Anti-maximal electro-shock	—	±	++
100	s.c.	4. Antagonism of leptazol-induced convulsions	Toxic	—	—
100	s.c.	5. Hot plate i, Direct effect	Toxic	++	++
		ii, + morphine { Addition / antagonism		—	—
100	Oral	6. Effects on phenylquinone-induced writhing	++g	++h	++i
25	Oral	7. Effects on food uptake	—	—	+j

++ Marked activity. + Moderate activity. ± Negligible activity. — Inactive. a. Slow jerky gait. b. Reduced reactivity. c. Slow rolling gait. d. Hypothermia of 2·6°. e. Hypothermia of 0·9°. f. Hypothermia of 0·5°. g. Effect > aspirin but 2/4 animals died. h. Effect > aspirin but 1/4 animals died. i. Effect > aspirin. j. 20% inhibition.

converted the monomethylamino derivative into 1,1-dimethyl-2-dimethylaminotetralin (II, R=NMe_2, R′=H), pale-yellow needles from ether, m.p. 77–78°. The title compounds were obtained by treating ethanolic solutions of the three bases prepared above with hydrogen chloride, and were recrystallized from ethanol-ether to afford colourless plates, plates and prisms, respectively, m.p. 219–221°, 227–231°, and 205–208°, respectively.

The results of the pharmacological screening of the three hydrochlorides, carried out using mice as test animals, are summarized in Table 1. Not atypically, it can be seen that the primary amine hydrochloride is the most toxic of the three compounds investigated and that the most promising analgesic activity (tests 5 and 6) appears to be associated with the tertiary amine hydrochloride: these two tests were therefore quantitated for this latter compound. Although the ED50 in test 5 was 12·0 mg/kg, in test 6 no dose regression occurred over the range 10–20 mg/kg, both dose-extremes of which induced a 60% inhibition of writhing. These observations, together with the results of tests 2, 3 and 7 (Table 1) indicate that the apparent analgesic activity of the tertiary amine hydrochloride is probably caused by its depressant action of the cns and not by its specific action at an analgesic receptor site.

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