Analgetics Based on the Pyrrolidine Ring. 9

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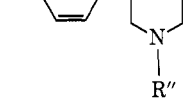
A series of *m*-(3-alkyl-1-allyl-3-pyrrolidinyl)phenols and related compounds has been synthesized for evaluation as potential nonaddicting analgesic drugs. The compounds have been tested in mice for their antinociceptive effect in an abdominal constriction (writhing) test and for their ability to antagonize morphine in the tail pressure test. The biological results are discussed in relation to chemical structure.

The interesting activity of a series of 1-(cyclopropylmethyl)pyrrolidines has been discussed in a previous paper of this series.[1] Replacement of the *N*-methyl group of profadol (Ia), a clinically effective analgetic[2] with an *N*-(cyclopropylmethyl) group, afforded an antinociceptive agent Ib that antagonized the analgesic effect of morphine in mice. As an extension of our work in this field we have prepared and examined the pharmacological properties of some *N*-allylpyrrolidines of type Ic.



Ia, R = H; R′ = Pr; R″ = Me
b, R = H; R′ = Pr; R″ = CH_2-c-C_3H_5
c, R = H; R′ = alkyl; R″ = $CH_2CH{=}CH_2$

The present paper describes the synthesis and examination of a number of such *N*-allylpyrrolidines. Like the *N*-(cyclopropylmethyl)pyrrolidines, many of these compounds have proved to be antinociceptive agents in an abdominal constriction (writhing) test in mice and simultaneously have the ability to antagonize the analgesic effects of morphine in a tail pressure test in the same species. Pertinent structure–activity relationships are discussed.

Chemistry and Experimental Section

The synthetic procedures used were similar to those reported previously[3-6] and are summarized below. The physicochemical properties of the compounds prepared for biological evaluation are listed in Table I.

3-Alkyl-1-allyl-3-(*m*-methoxyphenyl)pyrrolidines. Method A. Redistilled allyl bromide (0.1 mol) was added to the appropriate 3-alkyl-3-(*m*-methoxyphenyl)pyrrolidine (0.073 mol) and $NaHCO_3$ (10 g) in DMF (100 ml). The mixture was maintained at 50° overnight. The cooled mixture was evaporated to half-volume and filtered, H_2O (250 ml) was added, and the basic product was extracted into $CHCl_3$. The base was purified by distillation *in vacuo*. Alternatively, K_2CO_3 has been used instead of $NaHCO_3$.

***m*-(3-Alkyl-1-allyl-3-pyrrolidinyl)phenol Hydrochlorides. Method B.** 3-Alkyl-1-allyl-3-(*m*-methoxyphenyl)pyrrolidines were prepared as described in method A and O-demethylated with boron tribromide as reported earlier.[7,8] Where a 3-(*m*-isopropoxyphenyl)pyrrolidine was used, it was converted to the 3-pyrrolidinylphenol (compound 18) with refluxing 6 *N* HCl for 4 hr.

3-(*m*-Methoxyphenyl)-1-(3-methyl-2-butenyl)-3-propylpyrrolidine. Method C. 3-(*m*-Methoxyphenyl)-3-propylpyrrolidine was acylated with 3-methylcrotonyl chloride in the presence of NEt_3. Similar experiments have used CH_2Cl_2 as solvent, and in others, the acylation was carried out in the presence of anhydrous K_2CO_3 in DMF. The resulting amide was reduced to 3-(*m*-methoxyphenyl)-1-(3-methyl-2-butenyl)-3-propylpyrrolidine (compound 15) using $LiAlH_4$.

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***m*-[1-(3-Methyl-2-butenyl)-3-propyl-3-pyrrolidinyl]phenol. Method D.** 3-Propyl-3-(*m*-methoxyphenyl)pyrrolidine was acylated with 3-methylcrotonyl chloride and the resulting amide O-demethylated with boron tribromide. *m*-[1-(3-Methyl-2-butenyl-3-propyl-3-pyrrolidinyl]phenol (compound 16) was obtained on $LiAlH_4$ reduction of the crude amide.

[3-Isobutyl-1-(2-methylallyl)-3-pyrrolidinyl]phenols. Method E. 3-Isobutyl-3-(*m*-methoxyphenyl)pyrrolidine was N-acetylated with AcOH–Ac_2O. O-Demethylation with boron tribromide afforded *m*-(1-acetyl-3-isobutyl-3-pyrrolidinyl)phenol. A sample of the latter (20.5 g), 2*H*-3,4-dihydropyran (75 ml), and concentrated HCl (0.5 ml) were stirred at 50° for 1 hr, cooled, and allowed to stand overnight. Excess dihydropyran was distilled off and the residue, in Et_2O (200 ml), was washed with 2 *N* NaOH and H_2O, dried, and evaporated to give the crude *N*-acetyltetrahydropyranyl ether (28.5 g) which was refluxed with KOH (150 g) in EtOH (150 ml) and H_2O (150 ml) for 24 hr. EtOH was removed by distillation, H_2O (300 ml) added, and the pyrrolidine extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried, and evaporated. 3-Isobutyl-3-[*m*-[(tetrahydro-2*H*-pyran-2-yl)oxy]-phenyl]pyrrolidine was obtained as a pale yellow liquid (13.7 g), bp 164–170° (0.2 mm).

The above tetrahydropyranyl ether was converted to a 1-(2-methylallyl) derivative by alkylation with a 2-methylallyl halide in the presence of K_2CO_3 in DMF at room temperature (*cf.* method A). The tetrahydropyranyl protecting group was removed using 2 *N* H_2SO_4–EtOH (5:1) at 40° for 0.5 hr. The *m*-[3-isobutyl-1-(2-methylallyl)-3-pyrrolidinyl]phenol was isolated by conventional procedures.

Optical Resolution of *m*-(Allyl-3-isobutyl-3-pyrrolidinyl)-phenol. Method F. *m*-(1-Allyl-3-isobutyl-3-pyrrolidinyl)phenol was resolved by fractional crystallization of its salt with (−)-di-*p*-toluoyl-D-tartaric acid from EtOH. The salt of the (−) enantiomer crystallized first. Liberation of the base enriched in the (+) enantiomer from the salt in the mother liquors, followed by fractional crystallization of its salt with (+)-di-*p*-toluoyl-L-tartaric acid, led to the isolation of the (+) enantiomer. The resolved bases after liberation from their salts were each dissolved in EtOH and EtOH–HCl was added. The hydrochlorides, obtained on evaporation of the solution, were recrystallized from *i*-PrOH.

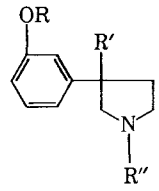
Pharmacological Methods. Antinociceptive activity was measured using the mouse abdominal constriction test,[9] in which acetylcholine (3.2 mg/kg) was the intraperitoneal challenge substance. Antimorphine activity was measured in a mouse tail pressure test based on the method of Bianchi and Franceschini,[10] using a special apparatus described by Collier.[11] The test drug was administered subcutaneously in solution together with a dose of morphine (22.2 mg/kg) having an antinociceptive effect in 95% of animals treated. A median effective antimorphine dose (ED_{50}) of the test drug was that increasing to 50% the proportion of animals showing a nociceptive response after morphine with the test drug.

The ED_{50} values for antinociceptive activity and antimorphine activity for the various compounds are listed in the Table I. Not less than ten mice were used at each dose level. Where the pyrrolidines were only available in the free-base form, aqueous solutions were prepared in the presence of 1 mol of D-tartaric acid.

Discussion

Examination of the biological results in Table I shows that many of these *N*-allylpyrrolidines show both antinociceptive and antimorphine activity in mice. This is in contrast to many piperidine analgesics where *N*-allyl substitution frequently fails to confer the dual activity on the compound.[12] However, the activity is often not so marked

Table I. *m*-(3-Alkyl-1-allyl-3-pyrrolidinyl)phenols and Related Compounds



No.	R	R′	R″	Method	Mp or bp (mm),[a] °C	Nature	Yield, %	Formula[b]	Antinocicpetive test, ED_{50}, mg/kg sc[r]	Morphine antagonism, ED_{50}, mg/kg sc[s]
1	Me	Pr	$CH_2CH{=}CH_2$	A	106–109 (0.2)	*d*	76	$C_{17}H_{25}NO$		
2	Me	Pr	$CH_2CH{=}CH_2$		143–144[c]	*e*, *f*		$C_{17}H_{26}ClNO$	20 (9.4–63)	>40
3	H	Me	$CH_2CH{=}CH_2$	B	151–153 (0.8)	*d*	80	$C_{14}H_{19}NO$	5.3 (3.4–9.3)	1.7 (1.0–2.6)
4	H	Et	$CH_2CH{=}CH_2$	B	141–143 (0.2)	*d*	27	$C_{15}H_{21}NO$		
5	H	Et	$CH_2CH{=}CH_2$		149–150[c]	*g*, *h*		$C_{15}H_{22}ClNO$	1.2 (0.67–2.6)	1.3 (0.77–2.0)
6	H	Pr	$CH_2CH{=}CH_2$	B	152–155 (0.5)	*d*	46	$C_{16}H_{23}NO$		
7	H	Pr	$CH_2CH{=}CH_2$		152–153[c]	*f*, *g*		$C_{16}H_{24}ClNO$	2.9 (1.8–4.8)	3.7 (2.2–6.5)
8	H	$CHMe_2$	$CH_2CH{=}CH_2$	B	161–162[c]	*f*, *i*	71	$C_{16}H_{24}ClNO$	2.5 (1.3–5.6)	2.5 (1.7–3.6)
9	H	CH_2CHMe_2	$CH_2CH{=}CH_2$	B	147–155 (0.3–0.4)	*d*	40	$C_{17}H_{25}NO$	0.63 (0.35–1.0)	3.4 (1.7–6.5)
10	H	CH_2CHMe_2	$CH_2CH{=}CH_2$		127–129[c]	*e*, *j*		$C_{17}H_{26}ClNO$	0.35 (0.19–0.49)	1.5 (0.77–3.2)
11	H	CH_2CHMe_2	$CH_2CH{=}CH_2$	F	149.5–150[c,k]	*e*, *m*		$C_{17}H_{26}ClNO$	0.12 (0.06–0.21)	0.57 (0.17–1.3)
12	H	CH_2CHMe_2	$CH_2CH{=}CH_2$	F	149.5–150[c,l]	*e*, *m*		$C_{17}H_{26}ClNO$	~10	>10
13	H	CHEtMe	$CH_2CH{=}CH_2$	B	155 (0.5)	*d*	69	$C_{17}H_{25}NO$	4.3 (2.0–9.2)	8.1 (4.4–18)
14	H	CH_2CMe_3	$CH_2CH{=}CH_2$	B	166–168 (0.6)	*d*	57	$C_{18}H_{27}NO$	0.47 (0.33–0.91)	1.6 (0.72–3.5)
15	Me	Pr	$CH_2CH{=}CMe_2$	C	140–148 (0.3)	*d*	41	$C_{19}H_{29}NO$	8.1 (5.4–11)	>40
16	H	Pr	$CH_2CH{=}CMe_2$	B, D	145–150 (0.15)	*d*	20, 50	$C_{18}H_{27}NO$[n]	4.5 (2.5–7.6)	>40
17	H	CH_2CHMe_2	$CH_2CH{=}CMe_2$	D	160–162 (0.15)	*d*	30	$C_{19}H_{29}NO$	1.7 (1.0–2.7)	>40
18	H	Pr	$CH_2CMe{=}CH_2$	B	128–130 (0.08)	*d*	36	$C_{17}H_{25}NO$[o]	8.1 (3.5–11.9)	16
19	H	CH_2CHMe_2	$CH_2CMe{=}CH_2$	E	150–152 (0.2)	*d*		$C_{18}H_{27}NO$	1.0 (0.56–1.9)	0.99 (0.37–2.8)
20	H	CH_2CHMe_2	$CH_2CMe{=}CHMe$[t]	D	162–164 (0.5)	*d*	35	$C_{19}H_{29}NO$	3.5 (1.9–9.6)	>20
21	H	CH_2CHMe_2	$CH_2CH{=}CHMe$[t]	E	170–174 (0.4)	*d*		$C_{18}H_{27}NO$	3.1 (2.0–4.9)	2.8 (1.6–5.7)
22	H	CH_2CHMe_2	$(CH_2)_2CH{=}CHCH_2Me$[u]	B	178–181 (0.3)	*d*	42	$C_{20}H_{31}NO$	1.6 (1.1–2.6)	>10
23	H	CH_2CHMe_2	$CH_2CH{=}CHCl$[u]	B	176–178 (0.5)	*d*	48	$C_{17}H_{24}ClNO$	0.17 (0.09–0.32)	Slight
24	H	CH_2CHMe_2	$CH_2CMe{=}CCl_2$	B	82–83.5	*p*, *q*	68	$C_{18}H_{25}Cl_2NO$	>2.5	Inactive 2.5
25	H	Pr	$CH_2C{\equiv}CH$	B	155–158 (0.3)	*d*	42	$C_{16}H_{21}NO$		
26	H	Pr	$CH_2C{\equiv}CH$		149–150[c]	*g*, *j*		$C_{16}H_{22}ClNO$	3.4 (2.5–4.6)	>40
Pentazocine[v]									2.7 (1.75–4.0)	6.2 (2.8–11.9)

[a] Melting points are corrected and were determined in a capillary tube (using a Townson and Mercer, Ltd., apparatus). Boiling points are uncorrected. Compounds were not resolved into their optical isomers unless indicated by a footnote in this column. [b] Microanalyses for C, H, and N were within ±0.4% of the theoretical values except where otherwise stated. [c] Hydrochloride prepared by addition of Et_2O–HCl to an Et_2O solution of the free base. [d] Oil or glass. [e] Needles. [f] From *i*-PrOH–Et_2O. [g] Microcrystalline. [h] From EtOH–Et_2O. [i] Cubes. [j] From EtOAc–Et_2O. [k] (−) enantiomer, $[\alpha]^{25}D$ −10.0° (EtOH, *c* 1.028 g/100 ml). [l] (+) enantiomer, $[\alpha]^{25}D$ +10.1° (EtOH, *c* 0.992 g/100 ml). [m] From *i*-PrOH. [n] C: calcd, 79.1; found, 78.3. Equivalent weight: calcd, 273; found, 270. [o] C: calcd, 78.7; found, 78.1. O: calcd, 7.2; found, 7.0. Equivalent weight: calcd, 259; found, 261. [p] Prisms. [q] From C_6H_6–petroleum ether (bp 60–80°). [r] The antinociceptive ED_{50} is the dose suppressing in 50% of T.O. strain mice the abdominal constriction response to intraperitoneal acetylcholine (3.2 mg/kg); 95% fiducial limits are indicated in parentheses. [s] The morphine antagonist ED_{50} is the dose suppressing in 50% of mice the antinociceptive effect of morphine (22.2 mg/kg subcutaneously) against the application of an artery clip to the base of the tail; 95% fiducial limits are indicated in parentheses. [t] Trans isomers. [u] The compounds tested were probably mixtures of cis and trans isomers. [v] References 9 and 13.

Table II. Comparison of Antinociceptive and Antimorphine Activities of *N*-Allyl- and *N*-Cyclopropylmethylpyrrolidines of General Formula I

R′ (formula I)	Antinociceptive activity, ED_{50}, mg/kg sc		Antimorphine activity, ED_{50}, mg/kg sc		Antimorphine ED_{50}/ antinociceptive ED_{34}	
	R″= $CH_2CH{=}CH_2$	R″= CH_2-c-C_3H_5	R″= $CH_2CH{=}CH_2$	R″= CH_2-c-C_3H_5	R″= $CH_2CH{=}CH_2$	R″= CH_2-c-C_3H_5
Me	5.3	20	1.7	0.9	0.32	0.045
Et	1.2	0.58	1.3	1.4	1.1	2.4
Pr	2.9	0.3	3.7	4.3	1.3	14.4
$CHMe_2$	2.5	0.76	2.5	3.0	1.0	4.0
CH_2CHMe_2[a]	0.35	0.11	1.5	1.7	4.3	15.4
CH_2CHMe_2[b]	0.12	0.06	0.57	1.1	4.75	18.2
CH_2CMe_3	0.47	0.19	1.6	3.3	3.4	17.2

[a] Racemate as succinate salt. [b] (−) enantiomer as succinate salt. Other details as in Table I.

in the *N*-allyl pyrrolidines as in the *N*-cyclopropylmethyl analogs.

A possible reference point for compounds of this type is pentazocine. The arbitary levels of activity proposed in the previous paper,[1] namely, an ED_{50} of less than 10 mg/kg subcutaneously in each test, were therefore taken to delineate the compounds of interest. This criterion gave ten compounds to be discussed (namely, **3**, **5**, **7**–**11**, **14**, **19**, and **21**). The first thing that was immediately apparent was that all of the compounds except two (namely, **19** and **21**) had unsubstituted allyl groups suggesting that substitution of the allyl generally had an unfavorable effect on activity, particularly on the antimorphine activity. Within the rather narrow range of comparison that is possible, these findings tend to bear out the trends found by Archer, *et al.*,[13] in their examination of pentazocine analogs for meperidine antagonist activity. *N*-(2-Propynyl) had a similar deleterious effect on activity and, as has been found in previous series of pyrrolidines, etherification of the phenol reduced the potency in both tests.

In Table II, the activities of a series of *m*-(3-alkyl-1-allyl-3-pyrrolidinyl)phenols are compared with those reported earlier[1] for the corresponding *N*-cyclopropylmethyl analogs. It is apparent in that with the exception of the 3-methylpyrrolidines, *N*-cyclopropylmethyl substitution gave rise to greater antinociceptive and slightly less antimorphine activity than did *N*-allyl substitution. It may be argued that the differences in the antimorphine activity in the two series were not really significant, but it is instructive to examine the last two columns of figures in Table II giving the ratios antimorphine ED_{50}/antinociceptive ED_{50}. This ratio was almost always lower in the *N*-allyl than in the *N*-cyclopropylmethyl series. Such a difference could well be of profound importance in the clinical usefulness of such an agent, particularly with respect to abuse liability. However, only clinical evaluation can provide an answer to such a question.

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