Agonist–Antagonist Actions and Stereoselectivity of Optical Pairs of Some *N*-Substituted α-*N*-Normetazocines

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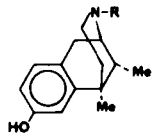
Abstract □ α-(−)-, (+)-, and (±)-*N*-4-Methylpentyl-, (−)- and (+)-*N*-*cis*-3-chloroallyl-, and (−)- and (+)-*N*-propynyl-*N*-normetazocine (I, II, and III, respectively) have been prepared from α-(−)-, (+)-, and (±)-*N*-normetazocine (IV) and tested for antinociceptive activity in mice and in morphine-dependent rhesus monkeys. The results obtained with Ia and b somewhat resemble the results obtained with the corresponding phenazocine isomers, whereas those observed with IIa and b more nearly correspond with those reported for (+)- and (−)-*N*-allyl-*N*-normetazocine (SKF 10,047; NANM). The propynyl isomers (IIIa and b) display profiles of activity more closely like the corresponding isomers of metazocine. Evidence is considered which suggests that some of the (+)-isomers merit closer scrutiny in animal and human studies.

Keyphrases □ α-Normetazocine—alkylation, optical pairs, antagonism, antinociception, psychotomimetic, mice, morphine-dependent rhesus monkeys □ Antagonists—α-normetazocine, alkylation, antinociception, psychotomimetic, mice, morphine-dependent rhesus monkeys

N-Substituted *N*-normetazocines of the α-series[1] (1) have attained importance not only in current medicine[2] but also in behavioral studies (2) and as receptor probes (3). Optical pairs are of particular interest (2–4). The present note describes the chemistry and some basic pharmacology of three optical pairs and one racemate belonging to the α-series.



I: R = $(CH_2)_3CHMe_2$
II: R = $CH_2CH{=}CHCl$ (Cis)
III: R = $CH_2C{\equiv}CH$
IV: R = H

a = (+), b = (−), c = (±)

EXPERIMENTAL SECTION

Chemistry[3]—The compounds were synthesized by alkylation of α-*N*-normetazocine (IV) using a tetrahydrofuran–dimethylformamide solvent mixture[4] and the halides 4-methylpentyl bromide for I, *cis*-1,3-dichloropropene for II, and propynyl chloride for III. Potassium carbonate or potassium bicarbonate was the hydrogen bromide or hydrogen chloride acceptor. Antipodes IIa and IIb were also prepared by optical resolution of α-(±)-3-*cis*-chloropropenyl-*N*-normetazocine (IIc) (5)[5] with *d*- and *l*-mandelic acids.

Mouse Antinociception Tests—Male mice weighing 20–30 g were used. All drugs were administered as salts, dissolved in distilled water, and administered subcutaneously in a volume of 0.1 mL/10 g of body weight. At least three doses per curve were tested and 6–10 animals per dose were used. ED_{50} values were calculated using computerized probit analysis.

Tail-Flick (TF) Tests—The procedure and modification (6) have been described. Briefly, the mouse tail was placed in a groove which contained a slit under which was a photoelectric cell. When the heat source or noxious stimulus was turned on, it focused on the tail and the animal responded by flicking its tail out of the groove. Thus, light passed through the slit and activated the photocell which, in turn, stopped the recording timer. The apparatus was calibrated so that control mice would flick their tails in 2–4 s. Mice were injected subcutaneously with drug and tested 20 min later. Vehicle controls were also tested.

In the antagonism experiments (tail-flick *versus* morphine), the antagonists were administered subcutaneously 10 min before morphine, and the animals were tested 20 min later.

Phenylquinone (PPQ) Abdominal Stretching Test (7)—The mice were injected subcutaneously with drugs and 10 min later received 2 mg/kg of a fresh *p*-phenylquinone solution intraperitoneally. The mice were then placed in cages in groups of two. At 10 min after the phenylquinone injection, the total number of stretches per group were counted within a 1-min period. A stretch was characterized by an elongation of the body, development of tension in the muscles in the abdominal region, and extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the phenylquinone-induced stretching response. Appropriate controls were used.

Hot Plate (HP) Assay (8)—The hot plate was held at a constant 55°C *via* a refluxing 1:1 mixture of ethyl formate and acetone. Mice were placed on the hot plate, and activity was noted as a delay of ≥5 s but no more than 30 s beyond the control time for the movement of the hind limb of the mouse, over at least two consecutive time periods. The mice were tested at 5, 10, 20, 30, 60 min, and longer if necessary, until responses returned to control levels.

Dependent Rhesus Monkey—In the single-dose substitution (SDS) test, for the most part, the recommendations of Seevers (9) and Seevers and Deneau (10) were utilized. A brief description of the procedure, including modifications (11), is as follows. Male and female rhesus monkeys (*Macaca mulatta*) weighing 2.5–7.5 kg were used. The animals were housed in pens, four or five to a group, and received 3 mg/kg sc of morphine every 6 h. This dose schedule was reported to produce maximal physical dependence (10). All the animals had received morphine for ≥3 months. A minimal, 2-week, wash-out and recuperation period was allowed for each animal between tests. The SDS test was initiated by the subcutaneous injection of the test drug or control substances (morphine and vehicle water, respectively) into the animals in a group that had not received morphine for 14–15 h and showed definite signs of withdrawal. Each animal was randomly allocated to one of four or five treatments: (*a*) two or three dose levels of the compound under investigation; (*b*) the morphine control, 3.0 mg/kg; (*c*) the vehicle control, 1 mL/kg. The animals were scored for suppression of withdrawal signs during a 2.5-h ob-

[1] α-Metazocine is 2′-hydroxy-2,5,9α-trimethyl-6,7-benzomorphan. For a comprehensive review and alternative chemical names for the 6,7-benzomorphans see Ref. 1.

[2] Pentazocine (see Refs. 1 and 5) is marketed as Talwin for both oral and parenteral use; phenazocine (Ref. 13) is sold in England as Narphen.

[3] Melting points (capillary, uncorrected, Table III) were taken in a Thomas–Hoover apparatus; mass spectral (molecular weights in agreement with theory) and C, H, and N data (Table III) are from the Section on Instrumentation and Analytical Services, National Institutes of Health. Optical rotations (Table III) were taken in a Perkin-Elmer 261 instrument using methanol as a solvent with the exception of IIIa and IIIb (bases) which were in ethanol. Rotation temperatures were 21–26°C. Free bases were recrystallized from acetone or acetone–hexane; hydrobromide salts were recrystallized from methanol–acetone. All compounds crystallized as white needles or prisms.

[4] This solvent mixture was suggested by Dr. H. Merz, C. H. Boehringer Sohn, Ingelheim, West Germany, who also kindly supplied 1,3-*cis*-dichloropropene.

[5] Compound IIc was supplied by Dr. A. E. Soria, Sterling-Winthrop Research Institute, Rensselaer, N.Y.

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Table I—Antinociceptive and Narcotic Antagonist Data for *N*-Substituted α-Normetazocine and Standards [a]

Compound	Antinociceptive Activity (ED_{50}), mg/kg sc			Antagonistic Activity (AD_{50}), mg/kg sc
	Tail-Flick Test	*p*-Phenylquinone Test	Hot Plate Test	Tail-Flick *versus* Morphine
Ia[b]	Inactive	16.3 (3.7-45.8)	70% at 100.0	Inactive
Ib[b]	20.6 (9.9-42.4)	0.9 (0.3-3.1)	3.1 (2.4-4.1)	Inactive
Ic[c]	10.8 (3.1-37.3)	5.1 (2.5-10.4)	8.3 (6.0-11.4)	Inactive
IIa[b]	Inactive	55% at 30	30% at 50.0	23.9 (17.6-32.6)
IIb[b]	Inactive	1.7 (0.5-5.9)	20% at 20.0	0.004 (0.002-0.008)
IIIa[b]	Inactive	Inactive	10% at 20.0	Inactive
IIIb[b]	Inactive	0.2 (0.1-0.4)	50% at 20.0	0.03 (0.1-0.7)
Morphine[d]	5.8 (5.7-5.9)	0.2 (0.2-0.3)	1.0 (0.8-1.1)	Inactive
Nalorphine[c]	Inactive	0.6 (0.3-1.4)	9.9 (5.7-17.1)	2.6 (0.7-9.8)

[a] Range of values is in parentheses. [b] Hydrobromide salt. [c] Hydrochloride salt. [d] Sulfate salt.

servation period. The observer was "blind" regarding the allocation of treatments. At the end of the study, the data were grouped according to dose and drug, and the results were analyzed using the Mann-Whitney U-test (12).

Precipitated Withdrawal (PPTW) Test in Rhesus-Monkeys—The PPTW test was performed under the conditions described above for the SDS test, except that the animals of a group were challenged 2 or 3 h after the last dose of morphine. Naloxone at a dose of 0.05 mg/kg sc served as the positive control.

(±)-5,9α-Dimethyl-2′-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan (Ic)—A mixture of 2.0 g of IVc (1, 13), 1.6 g of 4-methylpentyl bromide, 2.5 g of potassium bicarbonate, 4 mL of tetrahydrofuran, and 8 mL of dimethylformamide[4] was stirred at reflux for 2-3 h, cooled, diluted with 20-25 mL of water, and extracted with 30-40 mL of ether. The ether was washed twice with water, dried (sodium sulfate), and evaporated to dryness giving 1.9 g of Ic, mp 138.0-138.5°C after recrystallization[3].

The hydrochloride salt of Ic was prepared in acetone with hydrogen chloride. Compounds Ia and Ib were similarly prepared using IVa and IVb, respectively (14). The hydrobromide salts were prepared in acetone-33% hydrogen bromide in acetic acid.

Similarly, IIa and IIb were synthesized from IVa and IVb and *cis*-1,3-dichloropropane[4], and IIIa and IIIb were obtained from IVa and IVb and propynyl chloride; they were characterized as free bases and hydrobromide salts. Compounds IIa and IIb were also characterized as *d*- and *l*-mandelate salts, respectively.

Optical Resolution of α-(±)-2-(3-*cis*-Chloropropenyl)-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan (IIc)—A mixture of 4.3 g of IIc (5)[5], 2.6 g of *d*-mandelic acid, and 75 mL of absolute ethanol was heated until a solution was obtained and allowed to stand at room temperature for 4-5 h to give 2.5 g of the *d*-mandelate salt of IIa, mp 181-186°C. This was dissolved in 40 mL of boiling absolute ethanol. This solution deposited 2.0 g of pure IIa *d*-mandelate after standing overnight at room temperature. It was converted to 1.2 g of the base IIa by dissolving in boiling methanol (10 mL)-water (5 mL) and treating the solution with 5 mL of concentrated ammonium hydroxide, mp 136.0-138.5°C after a recrystallization from acetone-hexane.

Table II—Effects of *N*-Substituted Normetazocine in the Morphine-Dependent Rhesus Monkey

Compound	Single-Dose Substitution Test, mg/kg sc	Precipitated Withdrawal Test, mg/kg sc
Ia[a]	Did not substitute (3.0-12.0)	Weak activity; convulsions (6.0-18.0)
Ib[a]	Substituted completely (1.5-3.0)	Not tested
Ic[a]	Did not substitute; convulsions (12.0)	Not tested
IIa[a]	Did not substitute (0.25-4.0)	Did not precipitate withdrawal, 1.0-12.0 mg/kg
IIb[a]	Did not substitute (0.125-0.5)	Precipitated withdrawal (0.015-1.0)
IIIa[a]	Partial brief substitution (1.25-10.0)	Not tested
IIIb[a]	Did not substitute (0.015-0.25)	Precipitated withdrawal (0.125-0.5)
Morphine[b]	Substituted (3.0)	Did not precipitate withdrawal, (1.5-6.0)
Nalorphine[c]	Did not substitute (0.1-1.0)	Precipitated withdrawal (0.5)

[a] Hydrobromide salt. [b] Sulfate salt. [c] Hydrochloride salt.

The filtrates from isolation and recrystallization of the *d*-mandelate salt above were combined and evaporated to dryness under reduced pressure. The residue in warm methanol was treated with dilute ammonium hydroxide, affording 2.7 g of a mixture of IIa and IIb. This mixture, 1.7 g of *l*-mandelic acid and 30 mL of absolute ethanol, was heated to solution and left at room temperature for 4.5 h, affording 1.9 g of the *l*-mandelate salt of IIb, mp 181-186°C. This was dissolved in 20 mL of boiling absolute ethanol. The solution was concentrated to 12-15 mL and allowed to stand at room temperature overnight, affording 1.6 g of pure IIb *d*-mandelate which was converted to base IIb with methanol ammonium hydroxide as described for IIa above. Bases IIa and IIb and their mandelate salts were identical to those obtained from IVa and IVb, respectively, and *cis*-1,3-dichloropropene.

RESULTS

The different *N*-substituted normetazocines showed dissimilar profiles of activity (Tables I and II). None of the isomers nor the racemate of the *N*-4-methylpentyl-substituted normetazocine (Ia-c) showed antagonist activity *versus* morphine antinociception. Both the (−)-isomer and racemate were active in the TF, PPQ, and HP tests; the (−)-isomer was more potent than the racemate. In morphine-dependent monkeys, none of the compounds precipitated withdrawal and only the (−)-isomer substituted for morphine. The (+)-isomer and racemate produced convulsions, precluding testing at higher doses. Regarding the *N*-substituted chloroalkyl isomers, both IIa and b antagonized morphine antinociception; the (−)-isomer was clearly the more potent, ~50 times more so than nalorphine. Neither isomer was active in the TF or HP tests. In the PPQ test, the (−)-isomer was decidedly the more active antipode. Both isomers antagonized morphine antinociception; again, the (−)-isomer was far more potent. Neither isomer substituted for morphine in the addicted monkeys: the (−)-isomer, as expected, precipitated withdrawal, the (+)-isomer did not.

Finally, with the *N*-propynyl-substituted (+)- and (−)-normetazocines (IIIa,b) the following results were obtained. The (+)-isomer showed very weak activity in the HP test only and was devoid of antagonist activity. However, it partially substituted for morphine in addicted monkeys. The (−)-isomer showed weak agonist activity in the HP test and was equipotent with morphine in the PPQ test. As an antagonist, the (−)-isomer was much more active than nalorphine.

DISCUSSION

Results obtained with the 4-methylpentyl (I) isomers are vaguely reminiscent of those obtained with phenazocine antipodes (13), potency differences notwithstanding[6]. In both series, (−)-isomers supported morphine dependence although, relatively, a much larger dose of (−)-phenazocine was needed. Neither (+)-isomer would substitute for morphine, and with Ia severe tremors were noted. In retrospect, (+)-phenazocine, nearly as potent as morphine in the HP test, should have been tested more extensively.

Observations noted with the *N*-chloroallyl isomers (IIa,b) are quantitatively similar to those reported (15) for (+)- and (−)-*N*-allyl-*N*-normetazocine (NANM); IIb is a very powerful antagonist. It is interesting to note that Brady and co-workers recently showed (2) in rats and squirrel monkeys trained to discriminate the psychotomimetic phencyclidine hydrochloride (PCP) from saline that the (+)-isomer of NANM produced dose-dependent responses appropriate for PCP. The (−)-isomer did not produce responses appropriate for PCP at any dose. These data suggest a separation of psychotomimetic and

[6] Phenazocine is α-(±)-*N*-phenethyl-substituted *N*-normetazocine. It and its antipodes are 20-30 times more potent antinociceptively than corresponding I compounds.

Table III—Optical Rotation, Melting Points, and Analyses

Compound	$[\alpha]_D$	Concentration	mp, °C	Formula[a]
Ia	+100.1°	0.70	130-131	$C_{20}H_{31}NO$
Ia·HBr	+71.2°	0.87	229 230	$C_{20}H_{32}BrNO$
Ib	−99.5°	0.78	130-131	$C_{20}H_{31}BrNO$
Ib·HBr	+69.9°	0.67	229-230	$C_{20}H_{32}BrNO$
IIa	+115.8°	0.62	138-139[b]	—
IIa·HBr	+69.3°	0.49	199-200	$C_{17}H_{23}BrClNO$
IIa·*d*-Mandelate	+100.0°	0.78	186.0-187.5	—
IIb	−115.4°	0.95	137.0-138.5[c]	—
IIb·HBr	−68.9°	0.47	198-200	$C_{17}H_{23}BrClNO$
IIb·*l*-Mandelate	−99.7°	0.57	186-188	—
IIIa	+124.0°	0.23	167-169	—
IIIa·HBr	+90.9°	0.34	210-211	$C_{17}H_{22}BrNO$
IIIb	−124.0°	0.21	167-169	—
IIIb·HBr	−90.2°	0.35	210-211	$C_{17}H_{22}BrNO$
Ic	—	—	138.0-138.5	$C_{20}H_{31}NO$
Ic·HCl·H_2O	—	—	139-140	$C_{20}H_{32}ClNO·H_2O$

[a] All compounds were analyzed for C, H, and N; all values were within 0.4% of theoretical value. [b] Another crystalline modification melted at 115°C with gas evolution. [c] Another crystalline modification melted at 189-190°C.

analgesic effects. Whether in humans (−)-NANM or the chloroallyl *N*-substituted derivative are free of psychotomimetic effects remains to be shown. The racemate (IIc) was reported in 1964 (5), as was IIIc whose antipodes (IIIa,b) displayed profiles of activity reminiscent of *N*-methyl-6,7-benzomorphans of the α-series. This series was unique in two respects: (*a*) (+)-isomers substituted partially or completely for morphine; (*b*) the more antinociceptively potent (HP test) (−)-isomers would not. In fact, like IIIb, the (−)-isomers of this *N*-methyl series precipitated abstinence signs in morphine-dependent monkeys (4), yet two were more morphine-like than nalorphine-like in humans (16). In view of these different profiles of activity in animals and the remarkable separation of morphine-like effects in different species, these compounds [especially the (+)-isomers] deserve more extensive testing, perhaps in humans.

The exploitation of these differences may expand our knowledge of the basic mechanisms involved and possibly lead to a development of an ideal analgesic. It is also evident that studies with racemates may at times be misleading and that whenever possible pure optical isomers should be used.

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