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NOTES

α- and β-Halomorphides: Stereochemistry, Analgesic Potency, Toxicity, and Interaction with Narcotic Receptors *In Vitro*

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Abstract □ The configuration of the halogen on the C-ring of several α- and β-halomorphides was determined by NMR. The analgesic potencies of these halomorphides and their interactions with narcotic receptors in rat brain homogenate were measured, as was the toxicity of the α- and β-chloromorphides. The halomorphides were examined as possible irreversible binders to the narcotic receptor.

Keyphrases □ Halomorphides, α and β—NMR determination of configuration of halogen on C-ring, analgesic potencies, toxicity, interaction with narcotic receptors studied □ Stereochemistry—α- and β-halomorphides, NMR determination of configuration of halogen on C-ring □ NMR—determination of configuration of halogen on C-ring of α- and β-halomorphides □ Analgesic agents—potency of α- and β-halomorphides compared □ Toxicity—α- and β-halomorphides compared

Recently, β-chloromorphide was found as a constituent of a clandestine opiate sample and was identified by comparison with a known sample (physical properties and mass and IR spectra) (1). Apparently the toxicity of this compound is unknown and the configuration of the halogen is uncertain, although its preparation, physical properties, and some biological data were described (2, 3).

α-Chloromorphide was isolated in this laboratory from a reaction between morphine and dimethylchloroformiminium chloride. Samples[1] of the known α- and β-chloromorphides, as well as the β-bromo- and β-iodomorphides, were obtained, and their biological activities and NMR spectra were determined. (From the NMR spectra, the configuration of the halide about the C-6 and C-8 positions in the C-ring could be deduced.)

IR spectral data were used to differentiate α-substituted codides (substituted on the C-6 position of the C-ring of the codide) from the β-substituted compounds (C-8-substituted compounds) (4). A relatively strong band at 940 cm^{-1} characterized the α-compounds, in agreement with a previous report (4). The β-compounds possessed a 900-cm^{-1} band and a 935–940-cm^{-1} band (medium to weak). NMR was used to differentiate clearly the α- and β-halomorphides and to obtain the orientation of halogen on the C-ring.

[1] Samples were obtained from Dr. E. L. May, National Institutes of Health.

Table I—NMR Spectra of the α- and β-Halomorphides

Compound	δ[a], ppm: Proton Number 5	6	7	8	14	J, Hz: 5,6	5,7	5,8	6,7	6,8	7,8	8,14
α-Chloromorphide[b]	4.95	4.51	5.96	5.69	3.08	1.0	1.0	—	5.7	<1.0	9.6	1.8
β-Chloromorphide	4.96	5.71	5.86	4.0	2.54	3.3	—	1.4	10.4	2.2	1.4	9.9
β-Bromomorphide	5.16	5.72	6.05	4.19	3.16	3.3	—	1.6	10.4	2.3	1.8	9.6
β-Iodomorphide	5.14	5.82	5.93	4.07	2.96	3.0	—	1.8	10.2	1.9	1.2	9.8
Isocodeine	4.77	4.21	5.94	5.58	3.08	1.2	1.0	—	5.7	—	9.6	1.8
Codeine	4.85	4.14	5.67	5.26	2.66	6.4	1.3	—	1.8	3.1	10.0	2.3

[a] In deuterated methanol. [b] Probe at 50° to improve the solubility.

The α- and β-halomorphides were of interest also because it was found (5, 6) that thiol groups may exist at, or near, narcotic receptor sites (alkylating agents and heavy metals destroy receptor activity). Since the thiol, acting as a nucleophile, conceivably could interact with halomorphides, it was of interest to see whether these substrates would bind irreversibly with the narcotic receptor. Stork and Clarke (4) showed that the halomorphides, which are allylic halides, can react with various nucleophiles such as piperidine and thioethanol by an S_N2' mechanism. Thus, α-chloromorphide (I), β-chloromorphide (II), β-bromomorphide (III), and β-iodomorphide (IV) were examined for their ability to bind to the presumed narcotic receptors in rat brain homogenates and for analgesic potency *in vivo*. The α- and β-chloromorphides also were examined for acute toxicity in mice.

EXPERIMENTAL[2]

α-Chloromorphide (I)—Dimethylchloroformiminium chloride (7) (known to formylate phenols and alcohols) reacted exothermically with morphine hydrate (1.42 g, 0.05 mole) in dimethylformamide (10 ml). The yellow solution was stirred (20 min) and poured on ice, and a 10% solution of sodium carbonate was used to neutralize the solution. It was extracted with methylene chloride and dried over magnesium sulfate.

Removal of the solvent gave 1.7 g of a mixture of two compounds (by TLC). α-Chloromorphide (0.8 g) was isolated by utilizing its relative insolubility in hot acetone. The other compound in the mixture was formylmorphine, since prepared by other methods[1]. The I base was recrystallized from a mixture of acetone, methanol, and water, mp 192–194° [lit. (2) mp 193°]; mass spectrum: 303 (M^+), 305, and 268 (base).

Anal.—Calc. for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.24; H, 6.07; N, 4.35.

The other halomorphides were obtained from the original collection of Small and Lutz (2), who described their preparation and the preparation of the comparably substituted codides.

β-Chloromorphide (II)—The sample had a melting point of 184–188° [lit. (2) mp 188°]; mass spectrum: 303 (M^+), 305, and 268 (base).

Anal.—Calc. for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 66.93; H, 5.72; N, 4.38.

β-Bromomorphide Hydrochloride Monohydrate (III)—The sample was recrystallized from methanol–acetone, mp 191.5–193°; mass spectrum: 347 (M^+), 349, and 268 (base). It was dried for 20 hr at 100° before analysis.

Anal.—Calc. for $C_{17}H_{21}BrClNO_3$: C, 50.70; H, 5.26; N, 3.48. Found: C, 50.31; H, 5.22; N, 3.31.

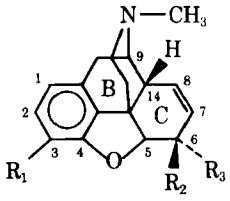
β-Iodomorphide Acid Tartrate Monohydrate (IV)—The sample was recrystallized from acetone–methanol, mp 148.5–152.5°; mass spectrum: 395 (M^+) and 268 (base).

Anal.—Calc. for $C_{21}H_{26}INO_9$: C, 44.77; H, 4.65; N, 2.49. Found: C, 44.88; H, 4.62; N, 2.41.

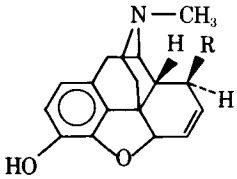
RESULTS AND DISCUSSION

Stereochemistry—The structure of the α-chloromorphide (I) isolated from the dimethylchloroformiminium chloride reaction was established by the comparison of its NMR, IR, and mass spectra and melting point with those of the known sample[2]. The configuration about C-6 was deduced from NMR data. The coupling constants associated with the C-5, C-6, C-7, C-8, and C-14 protons in I were nearly identical with those in isocodeine (V) (8, 9) (Table I) and quite different from those in codeine (VI). The pertinent protons of codeine (9) also are listed in Table I. The protons in I at C-5, C-6, and C-8 were deshielded, as anticipated, compared with isocodeine. Thus, I can confidently be placed in the 6-iso series, in which the chlorine atom is axially oriented on the C-ring of morphine (above the plane of the ring).

The NMR spectrum of β-chloromorphide (II) showed a considerable shift of several protons from their positions in codeine or isocodeine. The spectrum of II was consistent with the presence of the halogen at the C-8 position and the double-bond between C-6 and C-7. The coupling constant observed between the C-8 and



	R_1	R_2	R_3
I, α-chloromorphide	OH	Cl	H
V, isocodeine	OCH_3	OH	H
VI, codeine	OCH_3	H	OH
VII, morphine	OH	H	OH



	R
II, β-chloromorphide	Cl
III, β-bromomorphide hydrocloride	Br
IV, β-iodomorphide acid tartrate	I

[2] Melting points (Fisher-Johns apparatus) are corrected. IR data were obtained as Nujol mulls on a Perkin-Elmer 257 instrument. Mass spectra were from a Finnigan 1015D with a model 6000 data collection system, using electron impact (100 ev). NMR spectra were obtained in deuterated methanol on a Varian HA-100. The probe was maintained at 30°, except where indicated. Spin decoupling was obtained in the usual manner. Microanalyses were performed by the Laboratory of Chemistry's Section on Microanalytical Services and Instrumentation. Pharmacological assays were performed by Mrs. Louise Atwell, Medicinal Chemistry Section, Laboratory of Chemistry.

Table II—Analgesic Potency, Toxicity, and Receptor Binding Affinity of the α- and β-Halomorphides

Compound	ED_{50}[a,b]	O[c]	P[d]	D[e]	LD_{50}[a,b]	EC_{50}[f]
α-Chloromorphide[g]	0.07 (0.05—0.1)	3.8	15.9	121	49.7 (42.3—58.4)	7
β-Chloromorphide[g]	0.8 (0.5—1.1)	2.9	19.8	105	280.9 (247—320)	3
β-Bromomorphide hydrochloride	0.60 (0.44—0.83)	2.6	19.4	136	—	10
β-Iodomorphide acid tartrate	0.39 (0.27—0.56)	3.4	44.6	144	—	20
Morphine hydrochloride	1.2 (0.9—1.3)	3.8	28.2	145	576 (558—594)	3

[a] Numbers in parentheses represent 95% confidence limits as obtained by probit analysis. LD is the acute 24-hr toxicity (10 animals for each of four or five dose levels). [b] Subcutaneous injection in mice, milligrams per kilogram, using the hot-plate assay (see Refs. 11 and 12). [c] Onset of analgesia in minutes. [d] Peak time at which maximal analgesic response is observed in minutes. [e] Duration of analgesia in minutes. [f] Effective concentration of drug required to inhibit stereospecific ^{3}H-dihydromorphine binding to rat brain homogenate by 50% in nanomoles. [g] Base, dissolved in dilute hydrochloric acid.

C-14 protons (9.9 Hz) is indicative of an equatorially oriented chlorine atom (10) (in the plane of the ring, as opposed to the C-8 hydrogen atom which is axially oriented below the plane). The C-14 proton is known to be axially oriented on morphine's C-ring [J_{ax-ax} = 8–10 Hz (10)]. Double-irradiation experiments confirmed the observed couplings.

The NMR spectra of the β-bromo- and iodomorphides were very similar to the spectrum of the β-chloromorphide. The coupling constants observed between C-6 and C-7, C-7 and C-8, and C-5 and C-6 were nearly identical to those in β-chloromorphide. Therefore, they must also have their halides equatorially oriented on the C-ring at C-8.

The monograph of Small and Lutz (2) contains errors in the assignments of the position and the configuration of the halogen in the halomorphides. The alpha and beta nomenclature was originally conceived to denote configuration about the C-6 position in the codides. α-Chloromorphide, for example, was presumed to have the same configuration about the C-6 position as the hydroxyl has in morphine and codeine (equatorially oriented on the C-ring). β-Chloromorphide was presumed to have the reverse (axial) position at C-6 (2).

The alpha and beta nomenclature was retained in this paper to avoid confusion. However, the α-halogen designation in this paper relates to the C-6 iso configuration (axial orientation at C-6), and the β-designation relates to the C-8 equatorially substituted position. It is not possible to use "pseudo" or "allopseudo" nomenclature for C-8-substituted compounds in the morphine series, since the name "pseudomorphine" has been used to denote the C-2-coupled dimer of morphine (2). In the codeine series, the C-8-substituted compounds are denoted pseudohalocodides (allopseudo related to a C-8 iso compound).

Perhaps a more precise way of describing the position and configuration of the halogen would be to name α-chloromorphide as 6β-chloromorphide and β-chloromorphide as 8β-chloromorphide[3].

Pharmacology—*Analgesic Potency and Toxicity*—The β-chloro-, bromo-, and iodomorphides were generally more potent than morphine (Table II) in mice in the hot-plate test for analgesia (11, 12). The α-chloromorphide had 10–15 times the potency of morphine and was considerably more toxic in mice than was morphine or the β-chloromorphide (Table II).

Receptor Binding—When using the usual *in vitro* techniques (13) for measuring substrate binding to narcotic receptors from rat brain homogenates, only β-chloromorphide exhibited a binding affinity exactly comparable to morphine, although all of the compounds bound well to the receptors. Transport to the receptor *in vivo* may play an important part in the observed activity of these compounds. Whether for this or other reasons, these compounds generally do not exhibit binding affinity to the narcotic receptors in accord with their analgesic potencies *in vivo*.

None of these halomorphides was observed to bind irreversibly to the narcotic receptors *in vitro* in experiments where rat brain preparations were incubated with 10^{-6}–10^{-8} *M* halomorphide at 37° for up to 2 hr, washed, and then assayed for unreacted receptors.

SUMMARY AND CONCLUSIONS

The α- and β-halomorphides were found to have a C-6 axial and C-8 equatorial halide, respectively. These are potent analgesics *in vivo* with, presumably, all of the liabilities associated with morphine. Also, the toxicities of the examined chloromorphides were greater than morphine. Therefore, the presence of chloromorphide in illicit opiate samples would appear to present an additional hazard to opiate addicts.

The inability of these compounds to act as irreversible inhibitors of the narcotic receptors *in vitro* might be ascribable to the chemical stability of the various compounds or to a rapid equilibrium with the receptors (no one molecule of the analgesic may interact with the receptor long enough to undergo the irreversible reaction). Or, perhaps, the thiol groups, if present on the receptor, may be too far from the area of the primary interaction or may be inaccessable when the receptor is occupied by opiate.

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