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# Diastereoisomeric *N*-Tetrahydrofurfurylnoroxymorphones with Opioid Agonist–Antagonist Properties

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The two diastereoisomeric *N*-tetrahydrofurfurylnoroxymorphones and their hydrochlorides **1a** and **1b** have been prepared and studied pharmacologically. The *N*-(*R*)-tetrahydrofurfuryl derivative **1a** proved to be an opioid agonist–antagonist and the *N*-(*S*)-tetrahydrofurfuryl derivative **1b** a pure antagonist. As an analgesic, **1a** is 25 times more potent than morphine, but it does not show morphine-like side effects in mice. In withdrawn morphine-dependent rhesus monkeys, **1a** only partially suppresses abstinence. Its therapeutic ratio is exceptionally favorable compared with those of morphine and pentazocine. As antagonists, **1a** and **1b** have comparable potencies of 0.25 and 0.20 of that of nalorphine, respectively, in vivo. In vitro, however, **1a** is 28 times (guinea pig ileum) or 6.5 times (mouse vas deferens) more potent than **1b**. The antagonist properties of **1a** and **1b** were not anticipated according to known structure–activity relationships.

Recently, we have shown that stereoisomeric 5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans exert configuration-related non-morphine-like action profiles and that, in addition to well-known stereochemical requirements, the *R* configuration of the *N*-tetrahydrofurfuryl group is a major prerequisite for high analgesic potency.[1] We now wish to report on syntheses and pharmacological properties of the two diastereoisomeric *N*-tetrahydrofurfurylnoroxymorphone analogues **1a** and **1b** which, in contrast to the corresponding benzomorphans, surprisingly showed opioid agonist–antagonist properties.

**Chemistry.** The assigned configurations of **1a** and **1b** follow from their syntheses from noroxymorphone[2] and (*R*)- or (*S*)-tetrahydrofurfuryl bromide,[1] respectively. However, because of the cumbersome preparations of the optically active tetrahydrofurfuryl bromides, the use of the easily accessible (*R*)- and (*S*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonates for the alkylation of noroxymorphone is much more convenient. Other synthetic approaches will be published elsewhere.[3] The reaction products were isolated and purified by conventional laboratory procedures and crystallized as bases and as the corresponding hydrochlorides **1a** and **1b**.

**Pharmacological Results and Discussion.** The new compounds were tested for analgesia, morphine antagonism, Straub tail activity,[4] and toxicity in mice. Analgesia was studied using the Haffner tail-clip,[5] hot-plate,[6] and writhing[7] tests. $ED_{50}$ and $ED_{100}$ values were estimated by graphic evaluations of the dose–response curves. Acute toxicity was determined using $LD_{50}$ calculations according to Litchfield and Wilcoxon.[8] Morphine antagonist activity (suppression of morphine analgesia) was tested using a procedure[9] based on the tail-clip method. Agonist and antagonist potencies in vitro (myenteric plexus of guinea pig ileum and mouse vas deferens[10]) were assessed by Dr. Kosterlitz.[11] Morphine-like physical dependence capacity (suppression of abstinence in withdrawn, morphine-dependent rhesus monkeys[12]) was estimated by Dr. Harris and co-workers.[13] The pharmacological results obtained with **1a**, **1b**, and the standards morphine, nalorphine, pentazocine, and naloxone are summarized in Table I.

Although the diastereoisomers **1a** and **1b** (code numbers Mr 2096-CL and Mr 2097-CL) differ only in the configuration of their *N*-tetrahydrofurfuryl groups, they have quite different pharmacological profiles, **1a** being an agonist antagonist and **1b** a pure antagonist. Thus, in agreement with our earlier findings in the benzomorphan series,[1] analgesic activity is correlated with the *R* configuration of the *N*-tetrahydrofurfuryl substituent. In contrast to the benzomorphan analogues, however, relative analgesic potency (morphine = 1) of **1a** is more pronounced in the writhing than in the hot-plate test and barely present in the tail-clip test. Such a test-dependent differentiation of relative analgesic potency is typical for opioid agonist–antagonists[14] (compare **1a** with nalorphine and pentazocine). There is an excellent accordance of the potencies of **1a** in the writhing test (25.0 times that of morphine) and in the guinea pig ileum (24.6 times that of morphine). Both models are regarded as to be predictive for analgesic potencies of opioid agonist–antagonists in humans.[7,10,14] Compound **1a** does not elicit the Straub tail phenomenon[4] which has been reported[15] to be correlated with the addiction liability of morphine congeners. The fact that **1a** in a relatively high-dose range only partially suppresses morphine abstinence in rhesus monkeys[13] also suggests that the compound might have a low abuse potential in man. The therapeutic ratio ($LD_{50}/ED_{50}$, writhing test) of **1a** (47750) is exceptionally favorable when compared with those of morphine (1000) and pentazocine (157).

In contrast, the diastereoisomer **1b** is devoid of agonist activity in vivo and in vitro, thus being a pure antagonist like naloxone but much weaker in potency. As to their antagonist activities, **1a** and **1b** are comparable when tested vs. morphine in the tail-clip test, showing 0.25 and 0.20 of the potency of nalorphine, respectively. In the organ preparations, however, **1a** is much more active as an antagonist than **1b**, the relative potencies being 4.2 and 0.15 times nalorphine (guinea pig ileum) and 3.5 and 0.54 times nalorphine (mouse vas deferens). This apparent discrepancy may arise from the strong agonist component of **1a**, masking the antagonist effects of this substance in the intact animal.[16]

Table I. Pharmacological Data of the Diastereoisomeric *N*-Tetrahydrofurfurylnoroxymorphone Hydrochlorides



| Compd | Analgesia | | | | Toxicity,[f] $LD_{50}$, mg/kg sc, mice | Isolated organ,[g] rel potencies | | | Suppression of abstinence,[j] monkey |
|---|---|---|---|---|---|---|---|---|---|
| | Tail clip,[a] $ED_{50}$, mg/kg sc, mice | Hot plate,[b] $ED_{100}$, mg/kg sc, mice | Writhing,[c] $ED_{50}$, mg/kg sc, mice | Antagonism, tail clip,[d] $AD_{50}$, mg/kg sc, mice | Straub tail,[e] mice | | Agonism,[h] GPI | Antagonism[i] GPI | Antagonism[i] MVD | |
| 1a (Mr 2096-CL) | 200 | 1.9 | 0.02 | 4.0 | − | 955 (838-1088) | 24.6 | 4.2 | 3.5 | Partial[l] |
| 1b (Mr 2097-CL) | Inactive[k] | Inactive | Inactive | 5.0 | − | 810 (768-855) | 0 | 0.15 | 0.54 | No[l] |
| Morphine hydrochloride | 11.0 | 1.2 | 0.5 | | + | 500 (417-615) | 1.0 | 0 | | Yes[m] |
| Nalorphine hydrochloride | Inactive | Inactive | 0.5 | 1.0 | − | 560 (488-650) | 2.8 | 1.0 | | No[m] |
| Pentazocine hydrochloride | Inactive | 7.0 | 1.4 | 8.0 | − | 220 (190-255) | 0.27 | 0.3 | | No[n] |
| Naloxone hydrochloride | Inactive | Inactive | Inactive | 0.03 | − | 286 (255-320) | 0 | 3.8 | | No |

[a-f] For references to these methods, see the first paragraph of Pharmacological Results and Discussion. ED and AD values were estimated by graphical evaluations of the log dose–response curves obtained from experiments with three groups of animals per dose, the groups consisting of five (tail-clip test), ten (hot-plate test), and eight (writhing test) mice. [g] See ref 10. [h] Morphine = 1, see ref 11. [i] Nalorphine = 1, see ref 12. [j] See ref 11. [k] In this table inactive means that no effect was observed up to doses causing side effects. [l] See ref 13. [m] See ref 12. [n] See ref 21.

The antagonist properties of **1a** and **1b** were not anticipated. We have shown earlier[9] that *N*-furylmethyl substituents are able to confer antagonist properties to congeners of morphine (e.g., 5,9-dimethyl-2′-hydroxy-6,7-benzomorphans and noroxymorphone) and that this effect is correlated with the "allyl character" of those N-substituents. Consequently, saturation of the double bonds of the furan nucleus of such antagonists, leading to *N*-tetrahydrofurylmethyl analogues, should destroy antagonist activity. This proved to be true with the 5,9-dimethyl-2′-hydroxy-2-tetrahydrofurfuryl-6,7-benzomorphans.[1] The *N*-tetrahydrofurfurylnoroxymorphones **1a** and **1b**, however, did show antagonist actions in vivo and in vitro. Obviously, in appropriate morphine congeners, not only the "allylic" system of the *N*-furylmethyl substituent but also other common structural features of this group and its saturated analogue (most likely the ring oxygen) must be involved in drug–receptor interactions resulting in antagonist activity.[17]

## Experimental Section

Analyses (C, H, Cl, N, and S) agree with calculated values within ±0.4%. IR and NMR spectra are consistent with assigned structures. Optical rotations were measured in a Perkin-Elmer polarimeter 241. Uncorrected melting or decomposition points were taken in a Tottoli apparatus. For TLC silica gel plates (DC Fertigplatten Kieselgel 60 from Merck, Darmstadt) and $CHCl_3$–MeOH–concentrated $NH_4OH$ (95:5:0.1) were used (detection with iodine vapor).

**(+)-[(*S*)-Tetrahydrofurfuryl (1*S*)-Camphor-10-sulfonate] and (+)-[(*R*)-Tetrahydrofurfuryl (1*S*)-Camphor-10-sulfonate].** (+)-[(1*S*)-Camphor-10-sulfonyl chloride][18] (323.4 g, 1.25 mol) was added with stirring to 250 mL of absolute pyridine, cooled in an ice bath, followed by 102.1 g (1.0 mol) of tetrahydrofurfuryl alcohol within 30 min. After continuous stirring at room temperature for 20 h the reaction mixture was treated with 100 mL of $H_2O$ and poured into 2 L of ice water. The reaction products were separated by ether extraction; the combined ether extracts were washed twice with $H_2O$, 2 N HCl, and again twice with $H_2O$. After drying with $Na_2SO_4$ the solvent was removed at 50 °C, at last in vacuo. The residue was dissolved in 250 mL of $CCl_4$ and the solution diluted with petroleum ether (bp 40–80 °C) just until it became turbid. Crystallization was induced by seeding with the appropriate crystals grown separately. After 8 h at room temperature and 12 h at 0 °C, a crude product (152.0 g) melting at 55–56 °C was obtained, the mother liquor containing the other diastereoisomer. After three recrystallizations from $CCl_4$–petroleum ether (1:1) 109.5 g of pure (+)-[(*S*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate], crystallized with 0.25 mol of $CCl_4$, was obtained (30.9% based on tetrahydrofurfuryl alcohol): mp 67 °C; $[\alpha]^{25}_D$ +12.3° (*c* 1.0, EtOH). Anal. ($C_{15}H_{24}O_5S \cdot 0.25CCl_4$) C, H, Cl, S.

The mother liquor of the first crystallization was evaporated to dryness at 50 °C, at last in vacuo. A solution of the residue (185 g) in 185 mL of $CCl_4$–petroleum ether (1:1) yielded another crop of crystals when kept at −20 °C for 48 h. This process was repeated twice with prolonged storage at −20 °C (2 and 4 weeks). Finally, the mother liquor was evaporated at 50 °C, at last in vacuo, until the weight of the residue became constant. (+)-[(*R*)-Tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate] was obtained as an amber syrup: 97.0 g (30.7% based on tetrahydrofurfuryl alcohol); $[\alpha]^{25}_D$ +46.6° (*c* 1.0, EtOH). Anal. ($C_{15}H_{24}O_5S$) S.

Reaction of the diastereoisomeric camphorsulfonates with noroxymorphone and TLC of the reaction products proved to be a very sensitive test for their stereochemical purities. The observation of traces of **1b** formed along with the main reaction product **1a** in the following preparation of the latter clearly indicated that the syrupy camphorsulfonate contained traces of its diastereoisomer.[19]

**(−)-[*N*-[(*R*)-Tetrahydrofurfuryl]noroxymorphone Hydrochloride] (1a).** Noroxymorphone hydrochloride[2] (64.8 g, 0.20 mol), (+)-[(*R*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate] (69.6 g, 0.22 mol), $NaHCO_3$ (42.0 g, 0.50 mol), and NaI (29.8 g, 0.20 mol) were heated in 600 mL of absolute DMF with stirring at 100 °C

for 10 h. After evaporation to dryness in vacuo the residue was treated with $CHCl_3$ and $H_2O$. The $CHCl_3$ solution was separated, washed with $H_2O$, dried with $Na_2SO_4$, and evaporated to dryness in vacuo. A solution of the residue in 80 mL of 2.5 N ethanolic HCl yielded crystalline **1a** on standing at 0 °C overnight (26.7 g, 32.7%; $R_f$ 0.25, traces of **1b** at $R_f$ 0.30). For purification the crude hydrochloride was converted into the corresponding free base with $CHCl_3$, $H_2O$, and concentrated $NH_4OH$. The $CHCl_3$ extract was washed with $H_2O$, dried with $Na_2SO_4$, and evaporated to dryness in vacuo. Crystallization of the residue from 165 mL of EtOH–toluene (1:4) yielded (–)-[*N*-[(*R*)-tetrahydrofurfuryl]-noroxymorphone] (14.4 g, mp 217 °C). Recrystallization from EtOH–toluene (3:7) furnished the pure substance (10.0 g, mp 218 °C). Anal. ($C_{21}H_{25}NO_5$) C, H, N. The base (10.0 g, 0.027 mol) was dissolved in 125 mL of MeOH and 11.9 mL of 2.5 N ethanolic HCl (0.03 mol), and the solution was diluted with 250 mL of ether. After keeping at 0 °C overnight pure **1a** was obtained: 10.7 g (overall yield 13.1%); mp 321 °C dec; $[\alpha]^{25}_D$ –124.5° (*c* 1.0, EtOH). Anal. ($C_{21}H_{25}NO_5$·HCl) C, H, Cl, N.[20] Using the procedure described above, **1a** was also obtained from noroxymorphone hydrochloride[2] (0.02 mol) and (+)-(*R*)-tetrahydrofurfuryl bromide[1] (0.022 mol) in an overall yield of 11.5%.

**(–)-[*N*-[(*S*)-Tetrahydrofurfuryl]noroxymorphone Hydrochloride] (1b).** Noroxymorphone hydrochloride[2] (16.2 g, 0.05 mol), (+)-[(*S*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate] (19.5 g, 0.055 mol of the crystals containing 0.25 mol of $CCl_4$), $NaHCO_3$ (10.5 g, 0.125 mol), and NaI (7.5 g, 0.05 mol) were allowed to react as described above for **1a**. Crude **1b** was isolated from 30 mL of EtOH, 20.0 mL of 2.5 N ethanolic HCl (0.05 mol), and ether: 5.0 g (24.5%); $R_f$ 0.30, no **1a** detectable at $R_f$ 0.25. For purification 9.6 g of the crude hydrochloride **1b** (from the above and another preparation) was converted into the corresponding base with $CHCl_3$, $H_2O$, and $NH_4OH$. The $CHCl_3$ extract was washed with $H_2O$, dried with $Na_2SO_4$, and evaporated in vacuo. The residue crystallized from its solution in 55 mL of $CHCl_3$ and 6 mL of MeOH after dilution with 40 mL of ether–petroleum ether (1:1) yielding 8.0 g of (–)-[*N*-[(*S*)-tetrahydrofurfuryl]noroxymorphone], mp 125 °C dec. No satisfactory analyses were obtained because of undefined amounts of solvents included in the crystals. After recrystallization from toluene and drying at 80 °C and 0.01 mm for 8 h, 50 mg furnished crystals containing 0.5 mol of toluene (mp 87 °C). Anal. ($C_{21}H_{25}NO_5$·0.5$C_7H_8$) C, H, N. The main portion of the base with mp 125 °C (7.95 g) was converted into the hydrochloride with EtOH, 2.5 N ethanolic HCl, and ether as described above yielding 6.8 g (overall yield 16.7%) of **1b**: mp 318 °C dec; $[\alpha]^{25}_D$ –183.5° (*c* 1.0, EtOH). Anal. ($C_{21}H_{25}NO_5$·HCl) C, H, Cl, N.[20]

Using the procedure described above, **1b** was also obtained from noroxymorphone hydrochloride[2] (0.02 mol) and (–)-(*S*)-tetrahydrofurfuryl bromide[1] (0.022 mol) in an overall yield of 14.7%.

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(17) One of the reviewers considered interaction of the 14-hydroxy group with the saturated *N*-furylmethyl substituent as a possible factor leading to the antagonist properties of **1a** and **1b**. The fact that we have found antagonist properties also in *N*-[(*S*)-tetrahydrofurfuryl]normorphine, a congener of morphine lacking the 14-hydroxy group, should be an argument against this suggestion.
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(19) One of the reviewers suggested further purification of the syrupy (+)-[(*R*)-tetrahydrofurfuryl (1*S*)-camphor-10-sulfonate] (which is not necessary for the described preparation of **1a**). Purification was effected by column chromatography of 20 g of this compound using 400 g of aluminum oxide (neutral, activity grade III; Woelm, Eschwege). Elution with $CCl_4$–petroleum ether (1:1, 2400 mL), $CCl_4$ (3000 mL), and $CCl_4$–MeOH (98:2, 2000 mL) and evaporation of the corresponding fractions to dryness in vacuo afforded residues of 6.4, 3.9, and 6.6 g, the second one consisting of the entirely pure substance: nearly colorless syrup giving no traces of **1b** on reaction with noroxymorphone; $[\alpha]^{25}_D$ +41.6° (*c* 1.0, EtOH).
(20) As we stated at the beginning of the Experimental Section, the spectra of the new compounds are consistent with assigned structures. One of the reviewers missed references to the NMR spectra (which we had omitted because of the lack of relevant information). **1a** and **1b** are differentiated with regard to the >$NCH_2CH$– grouping, **1a** showing an $A_2X$ and **1b** an AB–X splitting. We thank Dr. K.-H. Pook and Mr. W. Pryss for measuring and interpretation of the spectra.
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