as yellow needles: NMR (CF_3COOH) δ 2.97 (s, 6, CH_3), 4.17 (s, 3, CH_3), 7.68 (s, 1, C_6-H), 9.39 (s, 1, C_4-H).

Method E. 2-Amino-*N*-amidino-5,7-dimethyl-1,8-naphthyridine-3-carboxamide (27). To a stirred solution of 0.20 g (8.70 mg-atom) of Na metal in 10 mL of anhydrous MeOH was added 0.80 g (8.37 mmol) of guanidine hydrochloride. After 5 min 0.465 g (2.01 mmol) of **24** was added. The mixture was refluxed for 1 h and the solvent removed. The cream solid was treated with H_2O and filtered to yield the crude product which recrystallized as cream flakes.

Method F. Ethyl 2-Amino-5,7-dimethyl-1,8-naphthyridine-3-carboxylate (25). A mixture of 0.900 g (6.0 mmol) of **4**, 1.358 g (12.0 mmol) of ethyl cyanoacetate, 0.20 g (1.5 mmol) of zinc chloride, and 10 mL of C_6H_6 was heated under reflux for 48 h with separation of water. The benzene suspension was washed with water, dried, and evaporated to yield 1.46 g (99%) of crude product, mp 235–238 °C, which on NMR analysis indicated 22% of **7** and 77% of **25**. Fractional crystallization from C_7H_8 afforded 0.195 g (16%) of **7** [NMR (CF_3COOH) δ 2.97 (s, 6, CH_3), 7.63 (s, 1, C_6-H), 9.00 (s, 1, C_4-H)] and 0.995 g (68%) of **25** [NMR (CF_3COOH) δ 1.52 (t, 3, $-CH_2CH_3$), 2.97 (s, 6, CH_3), 4.65 (q, 2, $-CH_2-$), 7.72 (s, 1, C_6-H), 9.40 (s, 1, C_4-H)].

Acknowledgments. The authors are indebted to the Medical Research Council of Canada for a research grant (MA-3150) in support of this work. We are grateful to Mrs. G. A. Haines and Mrs. S. L. Teplitsky for valuable technical assistance.

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Cardenolide Analogues. 2. 22-Methylenecard-14-enolides[1,2]

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Medical Foundation of Buffalo, Buffalo, New York 14203. *Received July 26, 1976*

22-Methylene-3β-hydroxy-5β,20(*S*)-card-14-enolide (**11**) and 22-methylene-3β-hydroxy-5β,20(*R*)-card-14-enolide (**12**) were synthesized from digitoxin (**1**). Attempts to prepare the 14β-hydroxy-22-methylene analogues were unsuccessful. The 20(*R*) isomer (**12**) was found in Na^+,K^+-ATPase inhibition studies to be twice as active as 14-dehydrodigitoxigenin (**17**). The 20(*S*) isomer (**11**) was significantly less active than **17**. The hydrolysis of steroid 3β-*tert*-butyldimethylsilyl ethers was also found to be much more difficult than with nonsteroids.

Cardenolides such as digitoxin (**1**) are very important in treating congestive heart failure.[3] The activity of analogues **2**[1], **3**[4], and **4**[4], the more reversibly acting AY-22 241 [3β-D-glucopyranosyl-14β,24-dihydroxy-21,23-bis-nor-5β-chol-20(22)-ene-20-carboxylic acid lactone (**5**)],[5-7] and current models of digitalis bonding[4,8] suggested to us the following features at C_{17} for new analogues in structure–activity studies: (1) increased reactivity or polarizability or (2) geometrically altered unsaturation. The 22-methylene analogues **6**, **11**, and **12** have these features. α-Methylene butyrolactones are quite reactive.[8,9] 14-Dehydrocardenolides retain significant albeit decreased Na^+,K^+-ATPase inhibiting activity.[10] Our efforts to synthesize **6** are continuing.

Chemistry. Digitoxin (**1**) was hydrolyzed to digitoxigenin **7**[11], hydrogenated to **8**[11], and converted to the *tert*-butyldimethylsilyl (*t*-$BuMe_2Si$) ether[12,13] **9**. Although the 22-methylene group could be added to **9** using the method used for the preparation of **11** and **12**, the *t*-$BuMe_2Si$ group could not be removed without the loss of the 14β-OH. Other protecting groups investigated either had the same disadvantages as the *t*-$BuMe_2Si$ or could not withstand the conditions used for the introduction of the 22-methylene group. Attempts to introduce the 22-methylene group in **8** were unsuccessful. Dehydration of **9** with thionyl chloride gave exclusively **13**. The enolate of **13** was treated with anhydrous CO_2[14] to give **14**, and reaction with aqueous formaldehyde and diethylamine[15] gave 20(*R*,*S*)-22-methylene lactone **15**.

Table I

	Yield of expected alcohol	
	With $(n\text{-Bu})_4\text{NF}$[b] in THF, 25 °C	With HOAc in H_2O-THF, 100 °C
15	<5%, 96 h[a]	65%, 13 h
16 (mp 186–187 °C)	<5%, 96 h[a]	78%, 9 h
Cholesterol 3β-*t*-$BuMe_2Si$ (mp 151–152 °C)	82%, 7 h	85%, 7 h

[a] The starting material decomposed when the reaction was heated at 100 °C. [b] Synthesis of $(n\text{-Bu})_4\text{NF}$ followed the method of Fowler et al.,[16] as modified by Corey.[12]

The acid-catalyzed hydrolysis of **15** to a mixture of **11** and **12** was unexpectedly slow (Table I). Tetra-*n*-butylammonium fluoride did not hydrolyze **15**, probably due

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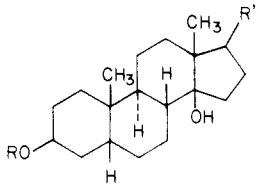
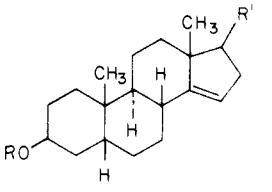
to the necessity of participation by the bulky ammonium ion in the hydrolysis.[17] By comparison, unhindered *t*-$BuMe_2Si$ ethers hydrolyze in 15–40 min.[12,13]

Separation of **11** and **12** was achieved with multiple fractional crystallizations, with purity followed by NMR using the definitive NMR studies of Ohga and Matsuo.[18] The absence of any 8(14) isomer in either **11** or **12** was confirmed by (1) the presence of a distinct C-15 vinyl proton in the NMR spectra of both compounds and the absence of any minor additional C_{19} peaks [since **17** and its 8(14) isomer[19] have different C_{19} absorptions[20]]; and (2) **17** was prepared under conditions analogous to those used for **11** and **12**, i.e., conversion of **7** to *t*-$BuMe_2Si$ ether **10**, thionyl chloride dehydration to **16**, and acid hydrolysis to **17**. No 8(14) isomer could be detected in the NMR of **17**.





	R	R′
1	digitoxose$_3$	
2	H	
3	H	
4	H	
5	glucose	
6	H	
7	H	
8	H	
9	*t*-$BuMe_2Si$	
10	*t*-$BuMe_2Si$	
11	H	
12	H	
13	*t*-$BuMe_2Si$	
14	*t*-$BuMe_2Si$	
15	*t*-$BuMe_2Si$	
16	*t*-$BuMe_2Si$	
17	H	

t-$BuMe_2Si = (CH_3)_3CSi(CH_3)_2-$

An x-ray crystallographic study of **12** was used to determine absolute configuration at C-20 as well as to confirm the assigned structure.[21]

Biology. The in vitro Na^+,K^+-ATPase inhibitory activities of **1**, **7**, **11**, **12**, and **17** were determined with rat brain Na^+,K^+-ATPase (E.C. 3.6.1.3.).[1,22,23] As shown in Table II, the 20(*R*) isomer **12** is about twice as active as **17** in inhibiting Na^+,K^+-ATPase, but the 20(*S*) isomer **11** is at least 50 times less active than **17**. (At concentrations greater than 1×10^{-4}, the bath preparation of enzyme and

Table II. Na^+,K^+-Dependent ATPase Inhibition Studies[a]

Steroid[d]	I_{50}, M, without preincubation	I_{50}, M, with 10-min preincubation[b]
17	$6.3 \pm 1.0 \times 10^{-5}$	$4.0 \pm 1.0 \times 10^{-5}$
12	$3.0 \pm 1.5 \times 10^{-5}$	$2.0 \pm 1.0 \times 10^{-5}$
11[c]	$>10^{-4}$	$>10^{-4}$
1	$7.0 \pm 1.5 \times 10^{-7}$	$2.4 \pm 0.8 \times 10^{-7}$
7	$4.6 \pm 1.6 \times 10^{-7}$	$5.0 \pm 1.7 \times 10^{-7}$
Ouabain	$5.0 \pm 0.6 \times 10^{-7}$	$4.0 \pm 1.0 \times 10^{-8}$

[a] I_{50} values are for two to four runs. Appropriate Mg^{2+} and Na^+ tubes were included to determine the basal activity of the Na^+,K^+-ATPase. This was then subtracted from activity in the presence of Mg^{2+}, Na^+, and K^+. [b] Steroid added to Na^+,K^+-ATPase medium lacking K^+ to allow the steroid and enzyme time to begin binding. After 10 min, KCl was added to begin Na^+,K^+-ATPase activity. [c] Precise value was not possible to obtain due to insolubility of the steroid in the medium. [d] The steroids were added in ethanol to the Na^+,K^+-ATPase tubes. In no case was more than 20 μL of ethanol added per tube. Independent studies showed that significant inhibition (over 3%) of the enzyme preparation by ethanol does not occur until over 25 μL of ethanol is added.

11 began to be cloudy.) Thus it appears that cardenolide receptors are very sensitive to changes in geometry in the C(17) side group and that geometry may be even more important than electronic factors. Additional evidence includes (a) the mediocre activity of our aldehyde **2** which, based on current mechanistic–electronic binding models, was predicted to be very active[1]; (b) the modified biological properties of AY-22 241 (**5**), which has a different orientation of the lactone ring relative to other cardenolides; and (c) the marked differences in activity between cardenolide analogue 17α and 17β isomers studied by Thomas.[4] We have also found that there may be two preferred orientations for cardenolide lactone rings, based upon x-ray crystallographic and subsequent conformational energy studies of **7**, **12**, **17**, and strophanthidin.[2,21] Further studies are in progress.

The inotropic activities of **11**, **12**, and **17** were assayed with guinea pig left atria using procedures we have previously reported.[1] However, the compounds were too insoluble in propylene glycol, so stock solutions were made in ethanol. Even after correction for ethanol depression, the three compounds were inactive up to 1×10^{-4} M. At higher concentrations, the bath solutions began to be cloudy, so any small inotropic activity could not be measured.

Experimental Section

Elemental analyses were performed by MHW Laboratories, Garden City, Mich. Mass spectra were obtained at the University of Minnesota Mass Spectroscopy Lab. Melting points were determined with a Thomas-Hoover melting point apparatus and are corrected. Thin-layer chromatographies (TLC) used reusable silica gel, glass bonded[24] "replates" (Shionogi Company, Osaka, Japan), using 10–20% ethyl acetate in petroleum ether (EtOAc–petroleum ether), or 100% $CHCl_3$, for alcohols or diols. Preparative TLC employed 1.25-mm silica gel HF_{254} (Brinkman), generally using 5–10% methanol in methylene chloride. "Usual work-up" included pouring the crude reaction mixture into ice and water; extraction three times with ether; washing the ether once with 3% HCl, once with water, once with 5% $NaHCO_3$, and once again with water; drying the ether over $MgSO_4$ or Na_2SO_4; and removing the ether at 35 °C in vacuo using a Büchi rotary evaporator. Crystallizations were done in EtOAc–petroleum ether unless noted otherwise. NMR assignment of C_{18}- and C_{19}-methyls with compounds having *t*-$BuMe_2Si$ ethers is tentative because the *tert*-butyl group obscures that region of the spectrum.

3β,14β-Dihydroxy-5β,14β,20ε-cardanolide 3β-*tert*-Butyldimethylsilyl Ether (9). A solution of 9.0 g (23.9 mmol) of **8**[11] was dissolved in a solution of 73 mL of anhydrous dimethyl-

formamide, 16.3 g (0.24 mol) of imidazole (Sigma Grade 1, dried in high vacuum 24 h), and 18.0 g (84 mmol) of *t*-$BuMe_2Si$ chloride (Willow Brook Labs) and stirred for 27 h at room temperature under N_2.[12] Usual work-up gave 10.1 g (86%) of **9**, mp 175–180 °C. In two out of five batches, TLC showed a trace of **13** but too little to be detected by NMR. (Attempts to purify these two batches by column chromatography resulted in the formation of detectable amounts of **13**.) The analytical sample of **9** was obtained by preparative TLC: mp 198–200 °C; IR ($CHCl_3$) 3600 (very small), 1770 cm^{-1}; NMR ($CDCl_3$) δ 4.4–3.95 (m, 2, C_{21}-H), 3.8 (m, 1, C_3-H), 250 (m, 2, C_{22}-H), 0.90 (s, 3, C_{19}-H), 0.85 [s, 12, C_{18}-H and $(CH_3)_3C$], 0.03 [s, 6, $(CH_3)_2Si$]. Anal. ($C_{29}H_{50}O_4Si$) C, H, Si.

3β-Hydroxy-5β,20ε-card-14-enolide 3β-*tert*-Butyldimethylsilyl Ether (13). To an ice-bath cooled solution of 12.3 g (25.0 mmol) of **9** in 100 mL of rapidly stirring anhydrous pyridine under N_2 was added 3.22 g (2.0 mL, 27.4 mmol) of $SOCl_2$. The solution was stirred in the ice bath for 1.25 h, followed by usual work-up (substituting 10% HC for 3% HCl) and crystallization to give 9.6 g (83%) of **13** showing very faint spot on TLC just below **13**. When this spot was collected by preparative TLC, it had turned into **13**, so it is presumed to be the C_{14}-SOCl ester. Data of **13**: mp 167–168 °C; IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) 5.1 (C_{15}-H), 4.4–3.95 (m, 2, C_{21}-H), 3.8 (m, 1, C_3-H), 2.40 (m, 2, C_{22}-H), 0.90 (s, 3, C_{19}-H), 0.85 [s, 12, C_{18}-H and $(CH_3)_3C$], 0.03 [s, 6, $Si(CH_3)_2$]. Anal. ($C_{29}H_{48}O_3Si$) C, H, Si.

3β-Hydroxy-22-carboxy-5β,20ε-card-14-enolide 3β-*tert*-Butyldimethylsilyl Ether (14). To an ice-bath cooled solution of 1.3 mL (1.01 g, 7.18 mmol) of isopropylcyclohexylamine in 25 mL of anhydrous tetrahydrofuran (THF) under N_2 was added 2.6 mL (7.30 mmol) of 2.82 M butyllithium. The solution was stirred for 10 min and cooled to −78 °C, and 2.20 g (4.57 mmol) of **13** in 20 mL of anhydrous THF was added over 5 min. After stirring for 40 min, the dry ice bath was removed, and immediately anhydrous CO_2 (Matheson, Bone-Dry grade) was bubbled into the solution until it warmed to room temperature over 40 min. The solution was poured onto 5% HCl and ice and extracted with ether; the ether solution was washed with water and dried. The ether was removed and the crude product crystallized to give 1.59 g (66%) of **14**: mp 139–144 °C; IR ($CDCl_3$) 1770, 1715 cm^{-1}; NMR ($CDCl_3$) δ 5.1 (C_{15}-H), 4.4–4.0 (m, 2, C_{21}-H), 3.75 (m, 1, C_3-H), 3.33 (m, 1, C_{22}-H), 0.91 (s, 3, C_{19}-H), 0.85 [s, 12, C_{18}-H and $(CH_3)_3CSi$], 0.03 [s, 6, $Si(CH_3)_2$]. Anal. ($C_{30}H_{48}O_5Si$) C, H, Si.

3β-Hydroxy-22-methylene-5β,20ε-card-14-enolide 3β-*tert*-Butyldimethylsilyl Ether (15). A solution of 7.07 g (13.7 mmol) of **14**, 30.8 mL of 37% aqueous CH_2O solution (Mallinckrodt, with 10% MeOH equivalent to 11.4 g, 380 mmol of CH_2O), and 8.80 mL (85 mmol, 6.22 g) of diethylamine was heated on a steam bath for 30 min. The solution was cooled and poured into a mixture of 5% HCl and ice. Usual work-up (but omitting HCl washes) and crystallization from MeOH–CH_2Cl_2 gave 5.98 g (90%) of **15**: mp 140–143 °C; IR ($CHCl_3$) 1755 cm^{-1}; NMR ($CDCl_3$) δ 6.36 [d, J_{HaHb} = 2 Hz, 1, C_{24}-H_b in 20(*S*) isomer], 6.32 [d, J_{HaHb} = 2 Hz, 1, C_{24}-H_b in 20(*R*) isomer], 5.72 [d, J_H = 2 Hz, 1, C_{24}-H_a in 20(*R*) isomer], 5.69 [d, J_{HaHb} = 2 Hz, 1, C_{24}-H_a in 20(*S*) isomer] (integration ratio of 6.36:6.32:5.72:5.69 was 6:4:4:6), 5.09 (br s, 1, C_{15}-H), 4.35–4.21 (br m, 2, C_{21}-H), 3.95 (m, 1, C_3-H), 3.3 (br m, 1, C_{20}-H), 0.91 (s, 3, C_{19}-H), 0.85 [br s, 12, C_{18}-H and $C(CH_3)$], 0.03 [s, 6, $Si(CH_3)_2$]; UV λ_{max} (EtOH) 204 nm (ϵ 8120). Anal. ($C_{30}H_{48}O_5Si$) C, H, Si.

22-Methylene-3β-hydroxy-5β,20(*S*)-card-14-enolide (11). A solution of 2.0 g (4.25 mmol) of **15**, 40 mL of THF, 70 mL of glacial HOAc, and 10 mL of water was heated on a steam bath for 13 h. Although at that time a small amount of **15** could be seen on TLC further heating did not remove **15** and would decrease the yield of **11** and **12**. The mixture was poured slowly into saturated $NaHCO_3$ and ice and extracted with ether, and the ether was washed with 5% $NaHCO_3$ until effervescence stopped, washed with water, and then dried. After removal of ether, the crude product was purified by column chromatography and crystallization to give 890 mg (65%) of a mixture of 40% **11** and 60% **12** (mp 145–151 °C) by NMR. Seed crystals of **11** were originally obtained by two successive preparative thin-layer chromatography runs (8% MeOH in CH_2Cl_2) and subjecting the resulting highly purified mixture of **11** and **12** to three fractional crystallizations. (Compounds **11** and **12** had identical R_f's in all thin-layer solvent systems examined, and separation was also not achieved on Corasil II with high-pressure liquid chromatography.) Using seed crystals in three fractional crystallizations, from 890 mg of the mixture, 110 mg of pure **11** was obtained: mp 192–193 °C; IR ($CHCl_3$) 3610 (small), 1755, 1200 cm^{-1}; NMR ($CDCl_3$) 6.32 (d, J_{HaHb} = 2 Hz, C_{24}-H_b), 5.72 (d, J_{HaHb} = 2 Hz, C_{24}-H_a), 5.22 (br s, 1, C_{15}-H), 4.44–4.32 (m, 2, C_{21}-H), 4.10 (m, 1, C_3-H), 3.28 (br m, 1, C_{20}-H), 1.00 (s, 3, C_{19}-H), 0.96 (s, 3, C_{18}-H); UV (EtOH) 204 nm (ϵ 8550); $[\alpha]^{26}_D$ −1° (*c* 0.059). Anal. ($C_{24}H_{34}O_3$) C, H; *m/e* calcd 370.2507, found 370.2484 (dev −2.3).

22-Methylene-3β-hydroxy-5β,20(*R*)-card-14-enolide (12). The remaining 710 mg of mother liquor from **11** (still containing **11** and **12**) was recrystallized three times using seed crystals of **12** (obtained as for **11**) to obtain 95 mg of **12** free of **11** by NMR. (The mother liquor still contained **11** and **12**.) Data of **12**: mp 215–217 °C; IR ($CHCl_3$) 3610 (small), 1755, 1200 cm^{-1}; NMR ($CDCl_3$) 6.36 (d, J_{HaHb} = 1 Hz, C_{24}-H_b), 5.69 (d, J_{HaHb} = 2 Hz, C_{24}-H_a), 5.20 (br s, 1, C_{15}-H), 4.50–4.34 (m, 2, C_{21}-H), 4.12 (m, 1, C_3-H), 1.00 (s, 3, C_{19}-H), 0.92 (s, 3, C_{18}-H); UV (EtOH) λ_{max} 204 nm (ϵ 8490); $[\alpha]^{26}_D$ +2° (*c* 0.055). Anal. ($C_{24}H_{34}O_3$) C, H; *m/e* calcd 370.2507, found 370.2542 (dev +3.5).

Acknowledgment. The financial assistance of the University of Minnesota Graduate School and College of Pharmacy, the Minnesota Heart Association, the Minnesota Medical Foundation, and the Veterans Administration Hospital is gratefully acknowledged. We are especially appreciative of the superb technical assistance of Mr. Gregory Quarforth in the Na^+,K^+-ATPase studies.

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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** (47 750) 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]