

36. Design and Synthesis of Novel Opiate Antagonists with LH-Stimulating Properties

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Opiate antagonists stimulate the release of LH and might, therefore, contribute to an innovative therapy for the treatment of numerous clinical syndromes characterized by hypofunction of the HHG axis. The purpose of this work was to design and synthesize pure opiate antagonists useful for this therapy. Me, Et, Pr, and PhCH₂ groups were introduced at the crucial 14 β -position of morphines and morphinans *via* a hetero-*Diels-Alder* key step starting from thebaine derivative **1** and tested for opiate antagonism and LH-stimulating activity. Me-, Et-, and Pr-substituted compounds **11a–c** were stronger antagonists than naltrexone, whereas Pr and PhCH₂ substituents in **11c**, **11d**, **9d**, **9d³**, **9d⁴**, and **9d⁵** led to orally active LH stimulators. Based on our finding that the μ -antagonists **12** and **11b⁵** showed no LH stimulation, we conclude that a combination of both μ - and κ -antagonism is necessary for potent LH stimulation.

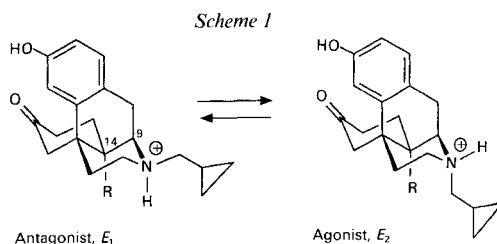
Introduction. – Endogenous opiate peptides (EOP's) of the CNS participate in the regulation of the hypothalamo-hypophyseal-gonadal (HHG) axis. In rodents as well as in primates, the administration of opiate agonists leads to suppression of the secretion of luteinizing hormone (LH), while on the other hand, increased release of LH follows the application of opiate antagonists [1]. Hypofunction of the HHG axis underlies numerous clinical syndromes such as the hypothalamic syndrome, idiopathic hypogonadotrophic hypogonadism, secondary hypothalamic hypogonadism, *Kallman's* syndrome, delayed puberty, adolescent menstrual disorders, anorexia nervosa, and stress-related disorders. The presently available therapeutic approaches – human gonadotrophin, anti-estrogens, and pulsatile LHRH – all have inherent drawbacks and limitations associated with them. Opiate antagonists as LH secretion stimulators, therefore, represent a potential novel approach to their treatment.

With the above background in mind, we have attempted to synthesize potent, long-acting, and orally active opiate antagonists as LH-secretion stimulators. In the present article, we describe the design, synthesis, and LH-stimulating activities of a series of novel 14 β -alkylated *N*-(cyclopropylmethyl)morphinans and -4,5 α -epoxymorphinans.

Design of Pure Opiate Antagonists. – Opiate antagonists with partial agonistic activity are of no interest as potential therapeutic agents for endocrine disorders, as they bear the danger of producing opioid side effects such as addiction or respiratory depression. We, therefore, deemed it necessary to design and develop pure opiate antagonists. The successful design of pure opiate antagonists is facilitated by the structure-activity relationships established over the past two decades. Replacement of an opiate *N*-methyl group in 14 β -unsubstituted morphinans, 4,5 α -epoxymorphinans, or 9 β -unsubstituted

benzomorphans by an *N*-allyl, *N*-cyclopropylmethyl, or *N*-(3-furyl)methyl group usually generates mixed opiate agonist-antagonists such as nalorphin, cyclorphan, levallorphan [13], cyclazocine, pentazocine [14], or MR 1452 [15]. If, however, the 14 β -position is simultaneously substituted by OH, MeO, EtO, Cl, Br, or RNH, relatively pure antagonists are obtained, *e.g.* naltrexone and naloxone (=17-(cyclopropylmethyl)-4,5 α -epoxy-3,14 β -dihydroxymorphinan-6-one and 4,5 α -epoxy-3,14 β -dihydroxy-17-(2-propenyl)-morphinan-6-one, resp.) [16]. The 9 β -unsubstituted benzomorphans, being transformed into nearly pure antagonists by the introduction of 9 β -OH or 9 β -alkyl groups [17], behave analogously.

The effect of the 14 β - and 9 β -substituents in increasing the relative degree of antagonism can be explained by a shift of the conformational equilibrium between axial and equatorial N-conformers in favor of the equatorial ones due to 1,3-diaxial steric hindrance between axial N-conformers and 14 β - (or 9 β)-substituents. This leads to the hypothesis (*Scheme 1*) that the equatorial conformation of the *N*-(cyclopropylmethyl) side chain is required for antagonist activity, while axial N-conformers confer agonist activity [18] [20] [24]. If this is correct the energy difference ΔE between axial and equatorial N-conformers may be taken as a measure for the purity of an opiate antagonist.



Hypothesis: The energy difference $\Delta E = E_2 - E_1$ determines the relative degree of opiate antagonism. High ΔE values give rise to highly pure opiate antagonists.

We have calculated ΔE values for several protonated morphines and morphinans (see *Table 2*, below) using SYBYL [19]¹⁾. For nalorphine, a mixed agonist-antagonist, a low $\Delta E = 0.55$ kcal/mol was obtained as expected. Naltrexone, a nearly pure antagonist, yielded a ΔE of 1.4 kcal/mol which was lower than expected (*Loew and Berkowitz*: 2.0 kcal/mol [20]). Replacement of the 14 β -OH group of naltrexone by a Me, Et, Pr, and PhCH₂ group resulted in considerably higher ΔE values (4–6 kcal/mol, see *Table 2*, below), implicating that antagonists of possibly higher purity than naltrexone might exist. In order to test this hypothesis, a series of novel 14 β -alkylated morphinans and 4,5 α -epoxymorphinans was prepared.

Chemistry. – A new method was developed for the introduction of β -alkyl groups at C(14) of morphinans and 4,5 α -epoxymorphinans starting from thebaine. The key step of

¹⁾ Minimum-energy conformations for equatorial and axial N-conformers (protonated) were calculated using SEARCH and MAXIMIN functions.

this synthetic sequence is the regio- and stereospecific hetero-*Diels-Alder* reaction of *N*-(cyclopropylmethyl)northebaine (**1**) with thioaldehydes $R'CHS$ formed *in situ* from thiosulfonates [23] (*Scheme 2, Exper. A*). The products **2a–d** of this cycloaddition were isolated in yields of 39–74% (*Table 1*). Direct desulfurization with *Raney*-Ni was only possible for **2d**: acidic workup after *Raney*-Ni treatment yielded **6d** in 25% yield (*Exper. J*). *Raney*-Ni treatment of **2a–c** in MeOH gave complex mixtures. A successful method for the desulfurization of **2a–d** was finally found *via* a rearrangement to the phenolic compounds **3a–d** with HBr at 0° (*Exper. B*). Again, only the 14 β -PhCH₂ derivative **3d** could be directly desulfurized (Li in liquid NH₃) to a 1:1 mixture **6d/5d** (*Exper. C*). Under the same conditions (*Exper. C*), **3a–c** gave only mercaptanes **4a–c** as a mixture of epimeric alcohols. Refluxing **3a–c** with *Raney*-Ni in MeOH gave S-free products, but they contained an additional cyclopropane ring due to formation of radical intermediates. However, **4a–c** could be desulfurized easily and in high yield by *Raney*-Ni (*Exper. D*) to **5a–c** without intramolecular formation of cyclopropanes. Finally, **5a–d** (mixture of epimeric alcohols) were reoxidized in high yield to the ketones **6a–d** (*Exper. E*) [8].

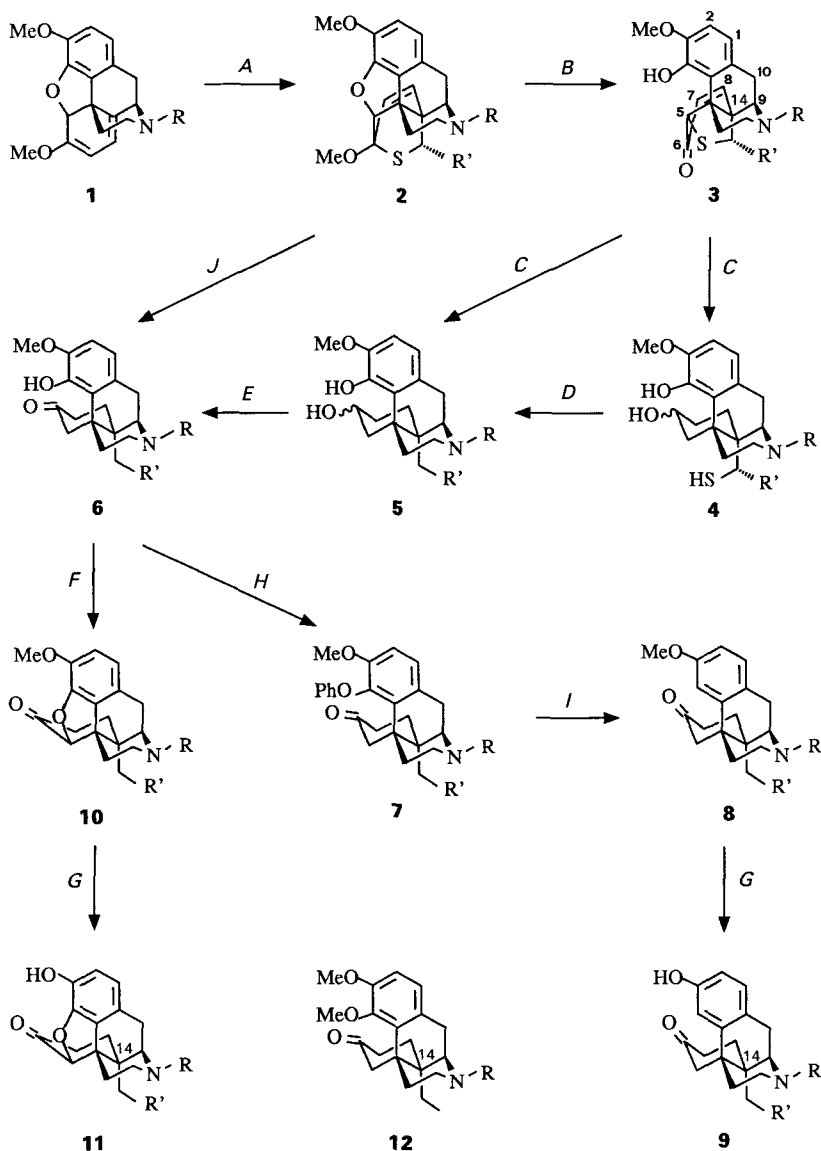
Elimination of the 4-OH group of **6b** and **6d** was achieved following a procedure of *Maeda et al.* [7]: **6b** and **6d** were first converted to the 4-phenyl ethers **7b** and **7d** (*Exper. H*) which, after acetalization, *Birch* reduction, and deacetalization (*Exper. I*) gave the desired 3-methoxymorphinan-6-ones **8b** and **8d**. Heating in pyridine hydrochloride at 170° for several h (*Exper. G*) [9] yielded phenols **9b** and **9d** in good yield. On the other hand, 4-hydroxy-3-methoxymorphinans **6a–d** were transformed by bromination, treatment with NaOH, and hydrogenation over Pd/C to 4,5 α -epoxymorphinans **10a–d** (*Exper. F*) [10] from which phenols **11a–d** were obtained as above (*Exper. G*). The 3,4-dimethoxymorphinan **12** was synthesized according to [11] from **6b**.

The 6-(methoxyfumaramido) derivatives **11b⁴** and **11b⁵** and **11c⁶** (see *Tables 1* and *2*), were prepared in analogy to [3] [5] from ketones **11b** and **11c**. Alcohols **9b⁴**, **9d⁴**, **9b⁵**, and **9d⁵** were obtained from **9b** and **9d** by NaBH₄ reduction in EtOH [4] [12]; the 6 α -isomers always predominated. The 6-deoxymorphinans **9b³** and **9d³** were prepared from the corresponding 6 α -alcohols **9b⁴** and **9d⁴** by dehydration with pyridine hydrochloride followed by hydrogenation over Pd/C (*Exper. K*). MeLi addition [2] [12] to ketones **11b–d** yielded the tertiary alcohols **11c²**, **11c³**, **11b³** and **11d³**; β -addition predominated clearly; **11c²** was the only α -addition product that could be isolated.

Results. – *Binding.* β -Configured Me, Et, and Pr groups at C(14) of 4,5 α -epoxymorphinans and morphinans resulted in compounds with very high affinity to both μ - and κ -receptors; the IC_{50} values (displacement of 3H-naloxone and 3H-bremazocine) for the 6-keto derivatives **11a–c** and **9b** were in the range of < 1 to 4 nM (*Table 2*). The introduction of a 14 β -PhCH₂ group led to a decrease in affinity, since both 6-keto derivatives **11d** and **9d** showed higher IC_{50} values: 1–14 nM. The 6-keto group represented the optimum functional group within all series; its reduction to α - and β -alcohols **9b⁴** and **9d⁴** and **9b⁵** and **9d⁵**, respectively, resulted in a slightly reduced affinity. The 6-unsubstituted compounds **9b³** and **9d³** had similar properties. Transformation of the 6-keto group into a 6 α -OH/6 β -Me moiety produced an even greater loss of affinity (**11b³**, **11c³**, **11d³**, and **9b²**). Elimination of the 4,5 α -epoxy O-atom in **11b**, **11b³**, and **11d** resulted in morphinans **9b**, **9b²**, and **9d** with increased binding affinity.

The most interesting binding properties were found for **12**, a 3,4-dimethoxymorphi-

Scheme 2



a R' = H (14-Me), **b** R' = Me (14-Et), **c** R' = Et (14-Pr), **d** R' = Ph (14-PhCH₂)

R = cyclopropylmethyl

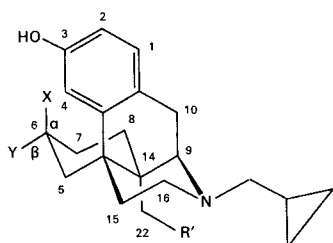
Exper. A: R'CH₂SS(O)CH₂R', toluene, reflux, 1 h. *Exper. B:* 48% HBr soln., r.t. *Exper. C:* Li/NH₃. *Exper. D:* Raney-Ni, MeOH, r.t. *Exper. E:* (COCl)₂, DMSO, NEt₃. *Exper. F:* 1) Br₂, AcOH; 2) 1N NaOH; 3) Pd/C, H₂, AcOH, H₂O. *Exper. G:* pyridine hydrochloride, 170°, 2.5 h. *Exper. H:* C₆H₅Br, Cu, pyridine, K₂CO₃, reflux, 17 h. *Exper. I:* 1) ethylene glycol, TsOH, benzene, reflux, 8 h; 2) Na/NH₃; 3) 1N HCl, reflux, 1 h. *Exper. J:* 1) Raney-Ni, MeOH, reflux, 23 h; 2) acetone/HCl. *Exper. K:* 1) pyridine hydrochloride, 175°, 1.5 h; 2) Pd/C, H₂, AcOH/H₂O, 18 h.

Table 1. *Synthesis of Compounds 2–12*

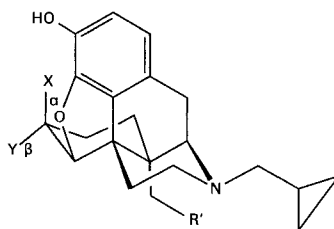
	R'	Exper.	Yield [%]	M.p. [°]	Formula
2a	H	<i>A</i>	39	167–168	C ₂₃ H ₂₇ NO ₃
b	Me	<i>A</i>	73	161–162	C ₂₄ H ₂₉ NO ₃ S
c	Et	<i>A</i>	63	156–157	C ₂₅ H ₃₁ NO ₃ S
d	Ph	<i>A</i>	74	149–150	C ₂₉ H ₃₁ NO ₃ S
3a	H	<i>B</i>	84	103–105	C ₂₂ H ₂₅ NO ₃ S
b	Me	<i>B</i>	83	256–258	C ₂₃ H ₂₇ NO ₃ S · HBr
c	Et	<i>B</i>	89	< 255	C ₂₄ H ₂₉ NO ₃ S · HBr
d	Ph	<i>B</i>	90	125–128	C ₂₈ H ₂₉ NO ₃ S
4a	H	<i>C</i>	58	oil	C ₂₂ H ₃₁ NO ₃ S
b	Me	<i>C</i>	87	oil	C ₂₃ H ₃₃ NO ₃ S
c	Et	<i>C</i>	89	oil	C ₂₄ H ₃₅ NO ₃ S
5a	H	<i>D</i>	77	oil	C ₂₂ H ₃₁ NO ₃
b	Me	<i>D</i>	89	oil	C ₂₃ H ₃₃ NO ₃
c	Et	<i>D</i>	65	oil	C ₂₄ H ₃₅ NO ₃
d	Ph	<i>C</i>	47	oil	C ₂₈ H ₃₅ NO ₃
6a	H	<i>E</i>	81	oil	C ₂₂ H ₂₉ NO ₃
b	Me	<i>E</i>	79	oil	C ₂₃ H ₃₁ NO ₃
c	Et	<i>E</i>	66	oil	C ₂₄ H ₃₃ NO ₃
d	Ph	<i>E, J</i>	68, 25	129–130	C ₂₈ H ₃₃ NO ₃
7b	Me	<i>H</i>	81	oil	C ₂₉ H ₃₅ NO ₃
d	Ph	<i>H</i>	60	oil	C ₃₄ H ₃₇ NO ₃
8b	Me	<i>I</i>	80	oil	C ₂₃ H ₃₁ NO ₂
d	Ph	<i>I</i>	57	168–169	C ₂₈ H ₃₃ NO ₂
9b	Me	<i>G</i>	88	130–131	C ₂₂ H ₂₉ NO ₂
b²	Me	[2] [12]	42	183–184	C ₂₃ H ₃₃ NO ₂ · C ₃ H ₄ O ₄
b³	Me	<i>K</i>	45	176–177	C ₂₂ H ₃₁ NO · C ₃ H ₄ O ₄
b⁴	Me	[4] [12]	50	233–235	C ₂₂ H ₃₁ NO ₂
b⁵	Me	[4] [12]	22	262–264	C ₂₂ H ₃₁ NO ₂ · HCl
d	Ph	<i>G</i>	82	189–190	C ₂₇ H ₃₁ NO ₂
d³	Ph	<i>K</i>	48	> 280	C ₂₇ H ₃₃ NO · HCl
d⁴	Ph	[4] [12]	72	235–236	C ₂₇ H ₃₃ NO ₂
d⁵	Ph	[4] [12]	9	> 280	C ₂₇ H ₃₃ NO ₂ · HCl
10a	H	<i>F</i>	83	100–102	C ₂₂ H ₂₇ NO ₃
b	Me	<i>F</i>	85	297–299	C ₂₃ H ₂₉ NO ₃ · HCl
c	Et	<i>F</i>	80	170–171	C ₂₄ H ₃₁ NO ₃
d	Ph	<i>F</i>	82	oil	C ₂₈ H ₃₁ NO ₃
11a	H	<i>G</i>	57	150–151	C ₂₁ H ₂₅ NO ₃
b	Me	<i>G</i>	66	157–158	C ₂₂ H ₂₇ NO ₃
b³	Me	[2] [12]	20	265–267	C ₂₃ H ₃₁ NO ₃ · HCl
b⁴	Me	[5] [3]	35, 51	233–236	C ₂₇ H ₃₄ N ₂ O ₅
b⁵	Me	[5] [3]	25, 50	> 300	C ₂₇ H ₃₄ N ₂ O ₅ · HCl
c	Et	<i>G</i>	74	> 280	C ₂₃ H ₂₉ NO ₃ · HCl
c²	Et	[2] [12]	4	> 280	C ₂₄ H ₃₃ NO ₃ · HCl
c³	Et	[2] [12]	48	250–253	C ₂₄ H ₃₃ NO ₃ · HCl
c⁶	Et	[5] [3]	38, 48	249–252	C ₂₈ H ₃₈ N ₂ O ₅
d	Ph	<i>G</i>	78	190–191	C ₂₇ H ₂₉ NO ₃
d³	Ph	[2] [12]	42	> 300	C ₂₈ H ₃₃ NO ₃ · HCl
12	Et	[11]	31	253–255	C ₂₄ H ₃₃ NO ₃ · HBr

Table 2. ΔE Values (see Introduction) and Pharmacological Results

ΔE [kcal/mol]	IC_{50} [nM] (3H-Naloxone)	IC_{50} [nM] (3H-Bremazocine)	AD_{50} [mg/kg i.v.] (Morphine)	AD_{50} [mg/kg i.v.] (EKC)	%LH stimulation (15 min, 5.6 mg/kg s.c.)	%LH stimulation (60 min, 5.6 mg/kg s.c.)	%LH stimulation (60 min, 32 mg/kg p.o.)
3.9	< 1	0.2	0.003	0.008	350	0	
9b ²	0.4	15.0	0.006	0.018	0		
9b ³	0.2	1.0	0.020	0.140	325		150
9b ⁴	0.1	< 1	0.040	0.056			0
9b ⁵	< 1	< 1	0.150	0.750			620
9d	< 1	5.0	0.050	0.200	670	430	700
9d ³	< 1	30.0	0.120	0.320			235
9d ⁴							570
9d ⁵	< 1	5.0	0.170	0.320			125
11a	0.2	4.0	0.005	> 0.05	975		
11b	< 1	0.2	0.005	0.010	520		
11b ³	5.0	38.0	0.010	0.100	1365		120
11b ⁴	< 1	5.0	> 1	> 1			
11b ⁵	< 1	7.0	0.056	5.000		0	
11c	< 0.1	0.7	0.004	0.020	1200	400	235
11c ²	0.1	1.7	0.002	> 0.032			0
11c ³			0.010	> 0.032	740	765	365
11c ⁶	0.5	5.0	0.400	>> 0.32			
11d	1.1	14.0	0.120	0.460	0	450	445
11d ³	4.0	38.0	0.010	0.400	260		
12	< 1	150.0	0.032	2.300	170	0	
Naltrexon	1.4		0.006	0.070	1300	450	500



- 9b** R' = Me, X, Y = =O
9b² R' = Me, X = α -OH, Y = β -Me
9b³ R' = Me, X = Y = H
9b⁴ R' = Me, X = α -OH, Y = β -H
9b⁵ R' = Me, X = α -H, Y = β -OH
9d R' = Ph, X, Y = =O
9d³ R' = Ph, X = Y = H
9d⁴ R' = Ph, X = α -OH, Y = β -H
9d⁵ R' = Ph, X = α -H, Y = β -OH



- 11a** R' = H, X, Y = =O
11b R' = Me, X, Y = =O
11b³ R' = Me, X = α -OH, Y = β -Me
11b⁴ R' = Me, X = α -MeOOCCH = CHCON(E), Y = β -H
11b⁵ R' = Me, X = α -H, Y = β -MeOOCCH = CHCON(E)
11c R' = Et, X, Y = =O
11c² R' = Et, X = α -Me, Y = β -OH
11c³ R' = Et, X = α -OH, Y = β -Me
11c⁶ R' = Et, X = α -MeOOCCH₂CH₂CON, Y = β -H
11d R' = Ph, X, Y = =O
11d³ R' = Ph, X = α -OH, Y = β -Me

nan derivative. It showed highest μ/κ differentiation with a μ/κ ratio > 150 and bound with < 1 nM to the μ -receptor, although it lacked a phenolic OH group.

Antagonism. μ - and κ -antagonistic properties were determined *in vivo* by reversing the analgesia induced by the μ - and κ -selective opiates morphine and ethylketocyclazocine (EKC). Opiate antagonism is influenced by 14β -substitution as follows: the 14β -OH group of naltrexone is not optimal; its replacement by Me, Et, or Pr groups (**11a–c**) led to antagonists with higher potency, Et and Pr representing the optimal chain length (see Table 2). The 14β -PhCH₂ substitution in **11d** gave rise to less pronounced antagonism. Transformation of the 6-keto groups of **11c** and **11d** into tertiary-alcohol moieties ($\rightarrow$ **11c²** and **11d³**) produced increased antagonistic potency: **11c²** was the strongest μ -antagonist of this series with an $AD_{50} = 0.002$ mg/kg *i.v.* All other modifications of the 6-keto group gave compounds with weaker antagonism. The transformation of the 6-keto group of **11b** into the isomeric 6-methoxyfumaramido derivatives **11b⁴** and **11b⁵** provided very interesting results. The 6α -isomer **11b⁴**, a close derivative of α -FNA [21], showed no detectable antagonistic properties, but rather was a potent analgesic with the following ED_{50} values (ED_{50} mg/kg; 1 h): tail flick *s.c.*, 13; hot plate *s.c.*, 0.4; hot plate *p.o.*, 5.0; arthritis *p.o.* (5 h), 1.8. An irreversible binding of **11b⁴** to the opiate receptor *via* 1,4-*Michael* addition is unlikely, as the saturated derivative **11c⁶** had the same analgesic properties and long duration of action. The 6β -isomer **11b⁵** (a close derivative of β -FNA [3]) proved to be a μ -antagonist with a μ/κ ratio of 89. Only the dimethoxy derivative **12** was nearly as selective with μ/κ 72. Morphinans **9b**, **9b²**, and **9d** were in general stronger antagonists than their corresponding 4,5 α -epoxymorphinan derivatives **11b**, **11b³**, and **11d**.

LH Stimulation. Antagonism of endogenous opiates results in increased LH release. As our IC_{50} and AD_{50} data were obtained by blocking exogenous opiates, no exact correlation between these data and LH stimulation can be expected. The most potent antagonists of this series (**11c²** and **9b**), being 3 (μ) to 10 (κ) times more potent than naltrexone, proved to be almost inactive as LH-inducers (see Table 2). Only 14β -Pr- (**11c**, **11c³**) and 14β -PhCH₂-substituted (**11d**, **9d**, **9d³**, **9d⁴**, and **9d⁵**) 4,5 α -epoxymorphinans and

morphinans were able to stimulate LH upon oral and subcutaneous application. The 14 β -Me- and 14 β -Et-substituted derivatives had a very short half life upon subcutaneous application. Based on its low toxicity and lack of opiate agonism (forced *i.v.* application of 6·1.8 mg/kg/d for 4 weeks, then 6·3.2 mg/kg/d for the next 4 weeks to rhesus monkeys, followed by naloxone challenge: 1.0 mg/kg *i.v.*), **9d** (SDZ 210–096) was selected for further development: it potently stimulated LH secretion following oral as well as subcutaneous application in the juvenile female rat, the adult male rat, and the adult female rat in both proestrus and diestrus stages [22]. The ED_{50} for stimulation of LH in juvenile female rats was < 1 mg/kg *p.o.*, 60 min following oral application. In addition to its LH-stimulating ability in the rat, **9d** proved to be a potent stimulator of LH in two non-rodent species, dog and monkey [22].

Discussion. – According to our hypothesis (*Scheme 1*), sterically demanding alkyl groups R, β -positioned at C(14) of *N*-(cyclopropylmethyl)morphinans or 4,5 α -epoxymorphinans, shift the conformational equilibrium between equatorial and axial *N*-conformers towards the equatorial (antagonistic) conformation of the *N*-(cyclopropylmethyl) group, thus providing pure opiate antagonists useful for therapy. This hypothesis could not be confirmed, since two compounds, **11b**⁴ and **11c**⁶, with relatively high axial-equatorial energy differences ($\Delta E \approx 4$ kcal/mol, see *Table 2*) proved to be potent opiate agonists in our assays. Obviously, the introduction of appropriate substituents such as methoxyfumaramido and methoxysuccinamido groups in α -position at C(6) of 4,5 α -epoxymorphinans provides potent opiate agonists despite the presence of the antagonistic *N*-(cyclopropylmethyl) side chain and a 14 β -Et group, forcing the former into an equatorial conformation.

Nevertheless, our hypothesis led to the synthesis and discovery of a series of potent and orally active opiate antagonists with LH-stimulating activity. Interestingly, most 14 β -PhCH₂ and 14 β -Pr derivatives turned out to be orally active antagonists and LH inducers, whereas 14 β -Me- and 14 β -Et-substituted compounds were orally inactive, although being potent antagonists upon intravenous application. Based on our finding that μ -antagonists with little κ -affinity such as **12** and **11b**⁵ showed no LH stimulation, we conclude that a combination of both μ - and κ -antagonism is necessary for potent LH stimulation.

Experimental Part

1. Pharmacology. 1.1. Reversal of the Analgesic Effect by Opiate Antagonists in the Tail-Flick Test in the Mouse.

Method: Mice (OF1 strain) weighing 20–25 g were placed in individual Perspex cylinders so that the tail of each animal protruded. A fixed point of the tail was exposed to a beam of radiant heat and the time in s elapsed before each mouse flicked its tail out of the path of the beam was recorded 30 and 15 min after subcutaneous administration of morphine (5.6 mg/kg) and ethylketocyclazocine (EKC; 0.56 mg/kg). This dose was sufficient to produce an analgesic response in 80–100% mice. Immediately after the 30 min post-drug measurement, a dose of the antagonist was administered intravenously (10 ml/kg) and the response time measured 30 min later (*i.e.* 60 min after administration of morphine or ethylketocyclazocine). The AD_{50} estimated graphically according to the method described by Litchfield and Wilcoxon (1949) was taken as the dose required to cause complete reversal of the analgesic response in 50% of the animals compared to controls which had been treated with saline and not antagonist.

1.2. LH Stimulation. Juvenile female rats of the Wistar strain were used. They were delivered to our animal quarters at 22–23 days of age and were used for experiments 2–4 days later. Average body weight at the time of an

experiment was 45 g. At sacrifice, trunk blood was collected on ice, and centrifuged at 4°. Sera were stored at –30°, for subsequent determinations of LH using specific RIA. The LH antiserum was produced in house and has been previously described [22].

1.3. *Opioid Receptor Binding*. Studies were carried out on crude rat brain homogenates (Sandoz OFA strain) essentially as described by Pasternak *et al.* [26] with minor modifications [25]. The affinities of the various ligands for 3H-naloxone and (–)-3H-bremazocine binding sites were determined by appropriately weighed regression analysis of Hill plots (at least four points covering four decades of concentrations). Both radioactive ligands were used at a concentration of 1 nM.

2. *Chemistry*. 2.1. *General*. Prep. flash column chromatography (FC): Merck silica gel 60 (230–400 mesh). M.p.: Büchi 510 melting point apparatus; uncorrected. Optical rotations: 1-dm cell, Perkin-Elmer-141 polarimeter. NMR spectra: Bruker WH-360; δ in ppm rel. to internal Me₄Si (δ = 0 ppm). Mass spectra: AEI MS 30 or MAT 212 under EI or FAB conditions. Microanalyses of crystalline compounds were within $\pm 0.4\%$ of theoretical values.

2.2. *Exper. A: 17-(Cyclopropylmethyl)-4,5 α -epoxy-3,6 α -dimethoxy-6 β ,14 β -(2-phenyl-1-thiaethane-1,2-diyl)-morphinan (2d)*. *N*-(Cyclopropylmethyl)norbaine [6] (1; 40.4 g; 0.115 mol) and *S*-benzyl phenylmethanethio-sulfinate [27] (21 g, 0.08 mol) were refluxed for 1 h in toluene (750 ml). The mixture was evaporated, mixed with H₂O, and extracted with Et₂O (3 $\times$). After drying (Na₂SO₄) and evaporation, recrystallization from Et₂O yielded **2d** (40.2 g, 74%) as white crystals. M.p. 149–150°. ¹H-NMR (CDCl₃, 100 MHz): 0.11–0.20 (*m*, 2 H); 0.45–0.68 (*m*, 2 H); 0.91–1.03 (*m*, 1 H); 1.93 (br. *d*, *J* = 12, H_{eq}-C(15)); 2.18–2.30 (*m*, H_{ax}-C(15), H_{ax}-C(16)); 2.35–2.47 (*m*, CH₂N, H_{ax}-C(10)); 3.05–3.15 (*m*, H-C(9), H_{eq}-C(10), H_{eq}-C(16)); 3.69 (*s*, CH₃O); 3.80 (*s*, CH₃O); 5.10 (*s*, H-C(5)); 5.27 (*d*, *J* = 10, H-C(18)); 5.75 (*s*, H-C(8)); 6.34 (*d*, *J* = 10, H-C(17)); 6.48 (*d*, *J* = 8, H-C(2)); 6.62 (*d*, *J* = 8, H-C(1)); 7.18–7.30 (*m*, 3 H); 7.40–7.45 (*m*, 2 H). MS: 473 (*M*⁺).

Similarly, **2a–c** were prepared: see Table 1.

2.3. *Exper. B: 17-(Cyclopropylmethyl)-4-hydroxy-3-methoxy-5 β ,14 β -(1-thiapropene-1,2-diyl)morphinan-6-one (3b)*. At r.t., **2b** (40.6 g, 99 mmol) was stirred into 48% HBr soln. (150 ml), whereby **2b** dissolved completely. As soon as **3b** started to crystallize, MeOH (60 ml) was added and the mixture stirred for 1 h at 0°. The product was filtered, washed with MeOH/Et₂O, and dried: **3b**·HBr (39.5 g, 83%). M.p. 256–258°. ¹H-NMR (CDCl₃, 360 MHz): 0.09–0.20 (*m*, 2 H); 0.47–0.6 (*m*, 2 H); 0.78–0.91 (*m*, 1 H); 1.21 (*d*, *J* = 8, CH₃); 1.53 (br. *d*, *J* = 12, H_{eq}-C(15)); 2.04 (*dt*, *J* = 12, H_{ax}-C(15)); 2.28–2.50 (*m*, H_{ax}-C(16), CH₂N); 2.63–2.77 (*m*, H_{ax}-C(10), H_{eq}-C(16)); 3.10 (*d*, H_{eq}-C(10)); 3.50 (*d*, *J* = 6, H-C(9)); 3.80 (*s*, CH₃O); 4.62 (*s*, H-C(5)); 4.73 (*q*, H β -C(17)); 5.81 (*s*, OH); 6.12 (*dd*, *J* = 12, 3, H-C(7)); 6.47–6.65 (*m*, H-C(1), H-C(2), H-C(8)). MS: 397 (*M*⁺).

Similarly, **3a**, **3c**, and **3d** were prepared: see Table 1.

2.4. *Exper. C: 17-(Cyclopropylmethyl)-14 β -(1-mercaptoethyl)-3-methoxymorphinan-4,6-diol (4b)*. Li (4.3 g, 0.62 mol) was dissolved in liq. NH₃ (1.8 l) at –50° and **3b** (22.5 g, 56.7 mmol) in THF (500 ml) added quickly to the deep blue soln. After 20 min at –40°, the soln. was broken down with solid NH₄Cl, NH₃ distilled off, and the residue taken up in H₂O and extracted with Et₂O (3 $\times$). Drying (Na₂SO₄), evaporation, and FC (AcOEt/hexanes 1:5) yielded **4b** (19.5 g, 87%; 6 α /6 β -mixture) as an oil.

Similarly, **4a**, **4c**, and **5d/6d** 1:1 were prepared: see Table 1.

2.5. *Exper. D: 17-(Cyclopropylmethyl)-14 β -ethyl-3-methoxymorphinan-4,6-diol (5b)*. A soln. of **4b** (13.4 g, 33.3 mmol) in MeOH (250 ml) was added rapidly under vigorous stirring to a suspension of Raney-Ni (130 g) in MeOH (1.5 l). After 15 min at r.t., the mixture was filtered, MeOH evaporated, and the residue taken up in CH₂Cl₂, dried (Na₂SO₄), and evaporated: **5b** (11.5 g, 89%; 6 α /6 β -mixture) as a light red foam.

Similarly, **5a** and **5c** were prepared: see Table 1.

2.6. *Exper. E: 14 β -Benzyl-17-(cyclopropylmethyl)-4-hydroxy-3-methoxymorphinan-6-one (6d)*. Oxalyl chloride (11.2 ml, 0.123 mol) was added at –60° to CH₂Cl₂ (1.08 l) and mixed with DMSO (18.4 ml, 0.26 mol) in CH₂Cl₂ (250 ml). At –78°, **5d** (51.2 g, 0.118 mol) in CH₂Cl₂ (235 ml) was added, and after 15 min at –55°, Et₃N (77 ml, 0.55 mol) was introduced and the mixture warmed up to –10°. H₂O was added and the mixture extracted with CH₂Cl₂ (2 $\times$). After drying (Na₂SO₄), evaporation and FC (AcOEt/hexanes 1:7 to 1:1), **6d** (34.6 g; 68%) was isolated as white crystals. M.p. 129–130°. [α] = –37.4 (*c* = 1, MeOH). ¹H-NMR (CDCl₃/D₂O, 360 MHz): 0.07–0.19 (*m*, 2 H); 0.47–0.64 (*m*, 2 H); 0.92–1.03 (*m*, 1 H); 1.58–1.81 (*m*, CH₂(8), H_{eq}-C(15)); 1.90–2.05 (*m*, CH-N, H_{ax}-C(16)); 2.19–2.28 (*m*, H_{eq}-C(7)); 2.33 (*dd*, *J* = 14, 5.6, H_{ax}-C(15)); 2.44–2.54 (*m*, H_{ax}-C(10), CH-N); 2.66 (*d*, *J* = 15, H_{ax}-C(5)); 2.68 (*d*, *J* = 5.5, H-C(9)); 2.70–2.79 (*m*, H_{ax}-C(7)); 2.83 (*d*, *J* = 18, H_{eq}-C(10)); 3.03 (br. *d*, *J* = 11, H_{eq}-C(16)); 3.05 (*d*, *J* = 12, H β -C(22)); 3.82 (*s*, CH₃O); 4.01 (*d*, *J* = 12, H α -C(22)); 4.28 (*dd*, *J* = 15, 1.5, H_{eq}-C(5)); 6.52 (*d*, *J* = 8, H-C(2)); 6.66 (*d*, *J* = 8, H-C(1)); 7.2–7.4 (*m*, 5 H). MS: 431 (*M*⁺).

Similarly, **6a–c** were prepared: see Table 1.

2.7. *Exper. F: 17-(Cyclopropylmethyl)-4,5 α -epoxy-14 β -ethyl-3-methoxymorphinan-6-one (10b).* At r.t., **6b** (14.6 g, 39.6 mmol) in AcOH (430 ml) was added dropwise within 30 min to a soln. of Br₂ (19 g, 119 mmol) in AcOH (200 ml). After 90 min, the mixture was evaporated, taken up in CH₂Cl₂ (1 l), and poured under stirring and cooling into 1N NaOH (300 ml). The org. phase was washed with H₂O and a little 10% tartaric acid (to pH 7), dried (Na₂SO₄), and evaporated. The residue was dissolved in AcOH (170 ml) and H₂O (130 ml) and hydrogenated over Pd/C (3 g) for 15 h at r.t. The mixture was filtered, evaporated, taken up in ice/2N Na₂CO₃, and extracted with CH₂Cl₂ (3 $\times$). Drying (Na₂SO₄) and evaporation of the org. phase gave, after FC (AcOEt/hexanes 1:5), **10b** (12.3 g, 85%). M.p. of **10b**·HCl, 297–299°. ¹H-NMR (CDCl₃, 90 MHz): 0.01–0.25 (*m*, 2 H); 0.40–0.65 (*m*, 2 H); 0.70–1.05 (*m*, with *t* at 0.94, *J* = 7, 4 H); 1.10–1.95 (*m*, 4 H); 2.05–2.75 (*m*, 8 H); 2.85–3.30 (*m*, 3 H); 3.88 (*s*, 3 H); 4.48 (*s*, H–C(5)); 6.58 (*d*, *J* = 8, 1 H); 6.70 (*d*, *J* = 8, 1 H).

Similarly, **10a**, **10c**, and **10d** were prepared: see Table 1.

2.8. *Exper. G: 14 β -Benzyl-17-(cyclopropylmethyl)-3-hydroxymorphinan-6-one (9d).* A mixture of **8d** (6.9 g, 16.7 mmol) and pyridine hydrochloride (30 g) was heated to 170° for 2 h. Fresh pyridine hydrochloride (15 g) was added and heating continued for 2 h. Pyridine hydrochloride (15 g) was again added and heating continued at 170° for 1.5 h. The mixture was taken up in H₂O and extracted with Et₂O (3 $\times$), yielding crude **9d** (6.4 g). FC (AcOEt/hexanes 1:7 to 1:2) gave **9d** (5.4 g, 82%) as colourless crystals. M.p. 189°. [α] = –71.4 (*c* = 1, MeOH). ¹H-NMR (CDCl₃, 360 MHz): 0.09–0.22 (*m*, 2 H); 0.47–0.65 (*m*, 2 H); 0.91–1.03 (*m*, 1 H); 1.15–1.23 (*m*, H_{eq}–C(15)); 1.55–1.71 (*m*, CH₂(8)); 1.97–2.11 (*m*, CH–N, H_{ax}–C(16)); 2.27 (*br. d*, *J* = 15.6, H_{eq}–C(7)); 2.32–2.43 (*m*, H_{ax}–C(15), H_{ax}–C(10)); 2.54 (*dd*, *J* = 12, 5, CH–N); 2.68–2.81 (*m*, H_{ax}–C(7), H–C(9)); 2.84–3.12 (*m*, H_{eq}–C(10), H–C(5), H_b–C(22), H_{eq}–C(16)); 4.09 (*d*, *J* = 12, H_a–C(22)); 6.63 (*dd*, *J* = 8, 3, H–C(2)); 6.85 (*d*, *J* = 3, H–C(4)); 6.89 (*d*, *J* = 8, H–C(1)); 7.2–7.5 (*m*, 5 H); 5.5–6.5 (*br. s*, OH). MS: 401 (*M*⁺).

Similarly, **9b** and **11a–d** were prepared: see Table 1.

2.9. *Exper. H: 14 β -Benzyl-17-(cyclopropylmethyl)-3-methoxy-4-phenoxy-morphinan-6-one (7d).* To a soln. of **6d** (12.5 g, 29 mmol) and bromobenzene (7.6 ml, 72.5 mmol) in pyridine (150 ml), powdered K₂CO₃ (12.2 g, 87 mmol) and Venus-Cu (3 g) were added. The mixture was refluxed for 17 h ($\rightarrow$ dark), then poured on ice/H₂O and extracted with Et₂O (3 $\times$). After drying (Na₂SO₄), evaporation, FC (AcOEt/hexanes 1:8 to 1:3), **7d** (8.9 g, 60%) and unreacted **6d** (3.2 g) were isolated.

Similarly, **7b** was prepared: see Table 1.

2.10. *Exper. I: 14 β -Benzyl-17-(cyclopropylmethyl)-3-methoxymorphinan-6-one (8d).* In a H₂O separator, **7d** (8.9 g, 7.5 mmol), ethylene glycol (30 ml, 0.538 mol), and TsOH (9.4 g, 50 mmol) were refluxed with benzene (800 ml) for 8 h. Then, 2N Na₂CO₃ (1 l) was added and the mixture extracted with benzene (2 $\times$). After drying (Na₂SO₄), the org. phase was evaporated: acetal of **7d** (9.4 g) as a white foam. This material was dissolved in toluene (250 ml) and added to liquid NH₃ (600 ml). Na (2.6 g, 113 mmol) was added in small pieces and the blue mixture stirred for 3.5 h at –55 to –35°. Solid NH₄Cl was added, NH₃ evaporated, and the residue taken up in H₂O and extracted with Et₂O (3 $\times$). The Et₂O phases were washed with 1N NaOH (2 $\times$) and H₂O (1 $\times$), dried (Na₂SO₄), and evaporated: acetal of **8d** (7.9 g) as a colourless oil. The latter was taken up in 1N HCl (1 l), refluxed for 1 h, and cooled to r.t. After addition of conc. NH₃ (to pH 10), the mixture was kept in the refrigerator overnight: **8d** (6.9 g, 57% overall from **7d**) as colourless crystals. M.p. 168–169°. [α] = –69.6 (*c* = 1, MeOH).

Similarly, **8b** was prepared: see Table 1.

2.11. *Exper. J: 14 β -Benzyl-17-(cyclopropylmethyl)-4-hydroxy-3-methoxymorphinan-6-one (6d).* A mixture of **2d** (10.2 g, 21.6 mmol), Raney-Ni (100 g), and MeOH (500 ml) was refluxed for 8 h. More Raney-Ni (50 g) was added and refluxing continued for 15 h. The mixture was filtered, Raney-Ni washed with MeOH (1 l), the MeOH evaporated, and the residue taken up in Et₂O, dried (Na₂SO₄), and evaporated. The resulting foam was dissolved in acetone/MeOH/HCl and warmed to 45° for 10 min, evaporated, taken up in 2N NH₃, and extracted with CH₂Cl₂ (3 $\times$). The resulting foam was purified by FC (AcOEt/hexanes 1:8): **6d** (2.3 g, 25%) as colourless crystals.

2.12. *Exper. K: 14 β -Benzyl-17-(cyclopropylmethyl)-3-hydroxymorphinan (9d³).* A mixture of **9d⁴** (2.2 g; 5.47 mmol) and pyridine hydrochloride (16 g) was heated to 175° for 1.5 h. A fresh portion of pyridine hydrochloride (11 g) was added and heating continued for 1.5 h. The mixture was taken up in ice/H₂O conc. NH₃ and extracted with Et₂O (3 $\times$). After drying (Na₂SO₄), evaporation, and purification by FC (CH₂Cl₂/MeOH/conc. NH₃ 98:2:0.2), the org. phase yielded 1.9 g of olefinic intermediate as a white foam. This foam was dissolved in AcOH/H₂O (75 ml/37 ml) and hydrogenated over 10% Pd/C (0.6 g) in a Parr apparatus for 18 h. After filtration, the residue was evaporated, taken up in ice/H₂O, made basic with conc. NH₃, extracted with Et₂O (3 $\times$), and purified by FC (AcOEt/hexanes 1:8 to 1:2): **9d³** (1.0 g, 48%) as colourless oil. M.p. of **9d³**·HCl > 280° (acetone/Et₂O). ¹H-NMR (CDCl₃, 360 MHz): 0.05–0.19 (*m*, 2 H); 0.42–0.61 (*m*, 2 H); 0.9–0.99 (*m*, 1 H); 1.03 (*br. d*, *J* = 14, H_{eq}–C(15)); 1.12–1.67 (*m*, 6 H); 1.85–2.10 (*m*, 4 H); 2.18–2.45 (*m*, 2 H); 2.48–2.58 (*m*, H–C(9), H_{ax}–C(10)); 2.82 (*d*, *J* = 19.5, H_{eq}–C(10)); 2.92–3.03 (*m*, H_{eq}–C(16)); 3.08 (*d*, *J* = 13.5, H_b–C(22)); 3.83 (*d*, *J* = 13.5, H_a–C(22));

4.0–5.2 (br. s, OH); 6.58 (dd, $J = 8, 3$ H–C(2)); 6.80 (d, $J = 3, 1$ H); 6.90 (d, $J = 8, \text{H–C}(1)$); 7.15–8.0 (m, 5 H). MS: 387 (M^+).

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