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

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(8.I.90)

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 $PhCH_2$ groups were introduced at the crucial 14β-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 $PhCH_2$ substituents in **11c**, **11d**, **9d**, **9d**[3], **9d**[4], and **9d**[5] led to orally active LH stimulators. Based on our finding that the μ-antagonists **12** and **11b**[5] showed no LH stimulation, we conclude that a combination of both μ- and $\varkappa$-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.

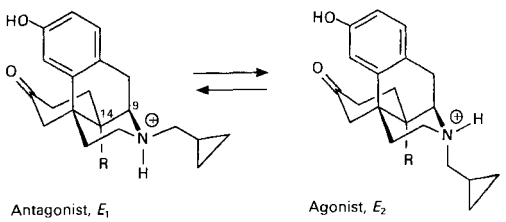
With the above background in mind, we have attempted to synthesize potent, long-acting, and orally active opiate antagonists as LH-secretion stimulators. In the present article, we describe the design, synthesis, and LH-stimulating activities of a series of novel 14β-alkylated *N*-(cyclopropylmethyl)morphinans and -4,5α-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 14β-unsubstituted morphinans, 4,5α-epoxymorphinans, or 9β-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 14β-position is simultaneously substituted by OH, MeO, EtO, Cl, Br, or RNH, relatively pure antagonists are obtained, *e.g.* naltrexone and naloxone (=17-(cyclopropylmethyl)-4,5α-epoxy-3,14β-dihydroxymorphinan-6-one and 4,5α-epoxy-3,14β-dihydroxy-17-(2-propenyl)-morphinan-6-one, resp.) [16]. The 9β-unsubstituted benzomorphans, being transformed into nearly pure antagonists by the introduction of 9β-OH or 9β-alkyl groups [17], behave analogously.

The effect of the 14β- and 9β-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 14β- (or 9β)-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.

Scheme 1



Antagonist, E_1 Agonist, E_2

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]). Replacemant of the 14β-OH group of naltrexone by a Me, Et, Pr, and $PhCH_2$ 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 14β-alkylated morphinans and 4,5α-epoxymorphinans was prepared.

Chemistry. – A new method was developed for the introduction of β-alkyl groups at C(14) of morphinans and 4,5α-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 thiosulfinates [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 14β-PhCH$_2$ derivative **3d** could be directly desulfurized (Li in liquid NH$_3$) 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].

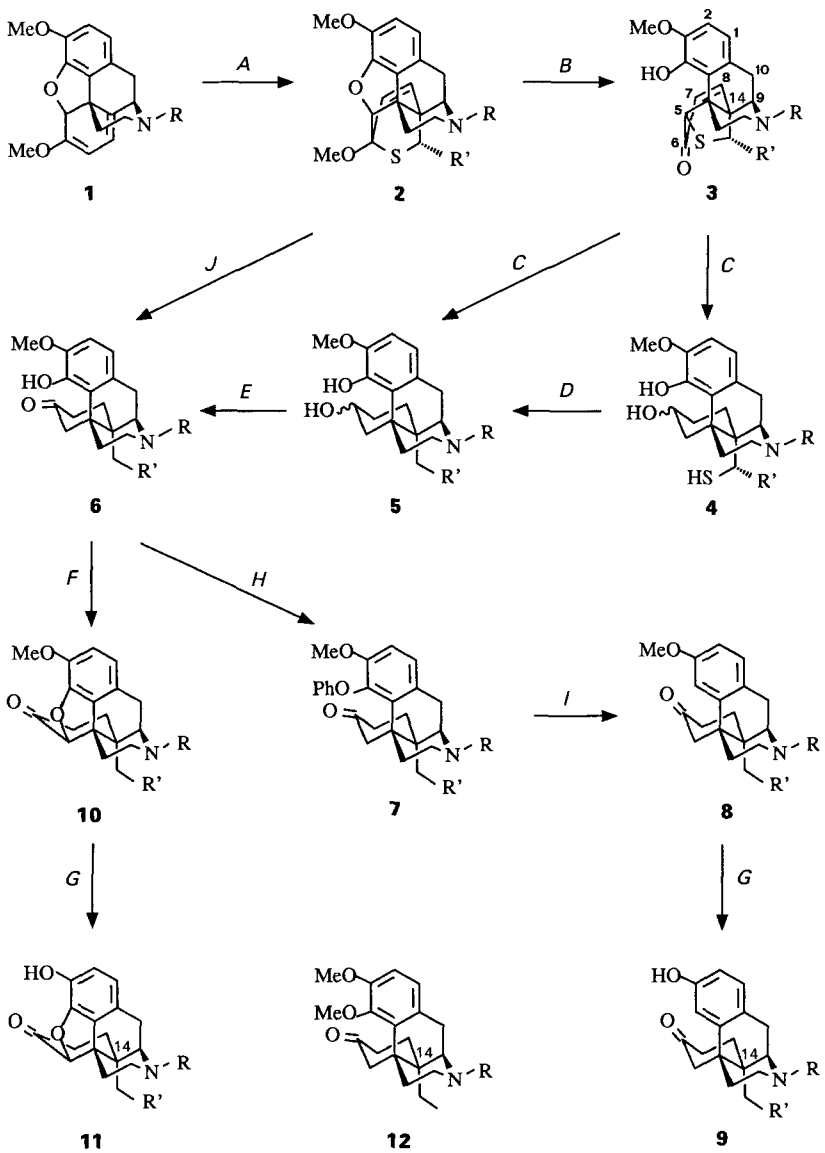
Elimination of the 4-OH group of **6b** and **6d** was achieved following a procedure of *Maeda et al.* [7]: **6b** and **6d** were first converted to the 4-phenyl ethers **7b** and **7d** *(Exper. H)* which, after acetalization, *Birch* reduction, and deacetalization *(Exper. I)* gave the desired 3-methoxymorphinan-6-ones **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 4,5α-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 **11b**[4] and **11b**[5] and **11c**[6] (see *Tables 1* and *2*), were prepared in analogy to [3] [5] form ketones **11b** and **11c**. Alcohols **9b**[4], **9d**[4], **9b**[5], and **9d**[5] were obtained from **9b** and **9d** by NaBH4 reduction in EtOH [4] [12]; the 6α-isomers always predominated. The 6-deoxymorphinans **9b**[3] and **9d**[3] were prepared from the corresponding 6α-alcohols **9b**[4] and **9d**[4] 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 **11c**[2], **11c**[3], **11b**[3] and **11d**[3]; β-addition predominated clearly; **11c**[2] was the only α-addition product that could be isolated.

Results. – *Binding*. β-Configurated Me, Et, and Pr groups at C(14) of 4,5α-epoxymorphinans and morphinans resulted in compounds with very high affinity to both μ- and $\varkappa$-receptors; the IC_{50} values (displacement of 3*H*-naloxone and 3*H*-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 14β-PhCH$_2$ 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 **9b**[4] and **9d**[4] and **9b**[5] and **9d**[5], respectively, resulted in a slightly reduced affinity. The 6-unsubstituted compounds **9b**[3] and **9d**[3] had similar properties. Transformation of the 6-keto group into a 6α-OH/6β-Me moiety produced an even greater loss of affinity (**11b**[3], **11c**[3], **11d**[3], and **9b**[2]). Elimination of the 4,5α-epoxy O-atom in **11b**, **11b**[3], and **11d** resulted in morphinans **9b**, **9b**[2], 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-$PhCH_2$)

R = cyclopropylmethyl

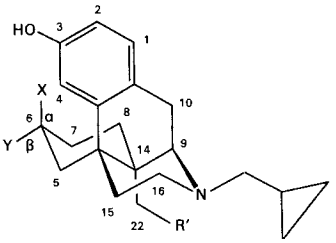
Exper. A: $R'CH_2SS(O)CH_2R'$, toluene, reflux, 1 h. *Exper. B:* 48% HBr soln., r.t. *Exper. C:* Li/NH_3. *Exper. D:* *Raney*-Ni, MeOH, r.t. *Exper. E:* $(COCl)_2$, DMSO, NEt_3. *Exper. F*: 1) Br_2, AcOH; 2) 1N NaOH; 3) Pd/C, H_2, AcOH, H_2O. *Exper. G*: pyridine hydrochloride, 170°, 2.5 h. *Exper. H*: C_6H_5Br, Cu, pyridine, K_2CO_3, reflux, 17 h. *Exper. I*: 1) ethylene glycol, TsOH, benzene, reflux, 8 h; 2) Na/NH_3; 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, H_2, $AcOH/H_2O$, 18 h.

Table 1. *Synthesis of Compounds* **2–12**

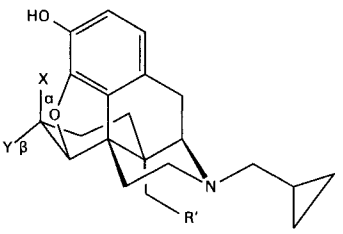
	R′	*Exper.*	Yield [%]	M.p. [°]	Formula
2a	H	*A*	39	167–168	$C_{23}H_{27}NO_3$
b	Me	*A*	73	161–162	$C_{24}H_{29}NO_3S$
c	Et	*A*	63	156–157	$C_{25}H_{31}NO_3S$
d	Ph	*A*	74	149–150	$C_{29}H_{31}NO_3S$
3a	H	*B*	84	103–105	$C_{22}H_{25}NO_3S$
b	Me	*B*	83	256–258	$C_{23}H_{27}NO_3S \cdot HBr$
c	Et	*B*	89	< 255	$C_{24}H_{29}NO_3S \cdot HBr$
d	Ph	*B*	90	125–128	$C_{28}H_{29}NO_3S$
4a	H	*C*	58	oil	$C_{22}H_{31}NO_3S$
b	Me	*C*	87	oil	$C_{23}H_{33}NO_3S$
c	Et	*C*	89	oil	$C_{24}H_{35}NO_3S$
5a	H	*D*	77	oil	$C_{22}H_{31}NO_3$
b	Me	*D*	89	oil	$C_{23}H_{33}NO_3$
c	Et	*D*	65	oil	$C_{24}H_{35}NO_3$
d	Ph	*C*	47	oil	$C_{28}H_{35}NO_3$
6a	H	*E*	81	oil	$C_{22}H_{29}NO_3$
b	Me	*E*	79	oil	$C_{23}H_{31}NO_3$
c	Et	*E*	66	oil	$C_{24}H_{33}NO_3$
d	Ph	*E, J*	68, 25	129–130	$C_{28}H_{33}NO_3$
7b	Me	*H*	81	oil	$C_{29}H_{35}NO_3$
d	Ph	*H*	60	oil	$C_{34}H_{37}NO_3$
8b	Me	*I*	80	oil	$C_{23}H_{31}NO_2$
d	Ph	*I*	57	168–169	$C_{28}H_{33}NO_2$
9b	Me	*G*	88	130–131	$C_{22}H_{29}NO_2$
b[2]	Me	[2] [12]	42	183–184	$C_{23}H_{33}NO_2 \cdot C_3H_4O_4$
b[3]	Me	*K*	45	176–177	$C_{22}H_{31}NO \cdot C_3H_4O_4$
b[4]	Me	[4] [12]	50	233–235	$C_{22}H_{31}NO_2$
b[5]	Me	[4] [12]	22	262–264	$C_{22}H_{31}NO_2 \cdot HCl$
d	Ph	*G*	82	189–190	$C_{27}H_{31}NO_2$
d[3]	Ph	*K*	48	> 280	$C_{27}H_{33}NO \cdot HCl$
d[4]	Ph	[4] [12]	72	235–236	$C_{27}H_{33}NO_2$
d[5]	Ph	[4] [12]	9	> 280	$C_{27}H_{33}NO_2 \cdot HCl$
10a	H	*F*	83	100–102	$C_{22}H_{27}NO_3$
b	Me	*F*	85	297–299	$C_{23}H_{29}NO_3 \cdot HCl$
c	Et	*F*	80	170–171	$C_{24}H_{31}NO_3$
d	Ph	*F*	82	oil	$C_{28}H_{31}NO_3$
11a	H	*G*	57	150–151	$C_{21}H_{25}NO_3$
b	Me	*G*	66	157–158	$C_{22}H_{27}NO_3$
b[3]	Me	[2] [12]	20	265–267	$C_{23}H_{31}NO_3 \cdot HCl$
b[4]	Me	[5] [3]	35, 51	233–236	$C_{27}H_{34}N_2O_5$
b[5]	Me	[5] [3]	25, 50	> 300	$C_{27}H_{34}N_2O_5 \cdot HCl$
c	Et	*G*	74	> 280	$C_{23}H_{29}NO_3 \cdot HCl$
c[2]	Et	[2] [12]	4	> 280	$C_{24}H_{33}NO_3 \cdot HCl$
c[3]	Et	[2] [12]	48	250–253	$C_{24}H_{33}NO_3 \cdot HCl$
c[6]	Et	[5] [3]	38, 48	249–252	$C_{28}H_{38}N_2O_5$
d	Ph	*G*	78	190–191	$C_{27}H_{29}NO_3$
d[3]	Ph	[2] [12]	42	> 300	$C_{28}H_{33}NO_3 \cdot HCl$
12	Et	[11]	31	253–255	$C_{24}H_{33}NO_3 \cdot HBr$

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

	ΔE [kcal/mol]	IC_{50} [nM] (3*H*-Naloxone)	IC_{50} [nM] (3*H*-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.*)
9b	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		
9b[4]		0.1	< 1	0.040	0.056			150
9b[5]		< 1	< 1	0.150	0.750			0
9d	4.8	< 1	5.0	0.050	0.200	670	430	620
9d[3]		< 1	30.0	0.120	0.320			700
9d[4]								235
9d[5]		< 1	5.0	0.170	0.320			570
11a	4.0	0.2	4.0	0.005	> 0.05	975		125
11b	4.5	< 1	0.2	0.005	0.010	520		
11b[3]		5.0	38.0	0.010	0.100	1365		120
11b[4]	*ca.* 4.0	< 1	5.0	> 1	> 1			
11b[5]		< 1	7.0	0.056	5.000		0	
11c	4.2	< 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]	*ca.* 4.0	0.5	5.0	0.400	≫ 0.32			
11d	6.1	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-MeOOCCH$_2$CH$_2$CON, Y = β-H
11d R' = Ph, X,Y = =O
11d³ R' = Ph, X = α-OH, Y = β-Me

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

Antagonism. μ- and $\varkappa$-antagonistic properties were determined *in vivo* by reversing the analgesia induced by the μ- and $\varkappa$-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-PhCH$_2$ substitution in **11d** gave rise to less pronounced antagonism. Transformation of the 6-keto groups of **11c** and **11d** into tertiary-alcohol moieties (→ **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 $\mu/\varkappa$ ratio of 89. Only the dimethoxy derivative **12** was nearly as selective with $\mu/\varkappa$ 72. Morphinans **9b**, **9b²**, and **9d** were in general stronger antagonists than their corresponding 4,5α-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-PhCH$_2$-substituted (**11d**, **9d**, **9d³**, **9d⁴**, and **9d⁵**) 4,5α-epoxymorphinans and

morphinans were able to stimulate LH upon oral and subcutaneous application. The 14β-Me- and 14β-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 -4,5α-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 4,5α-epoxymorphinans provides potent opiate agonists despite the presence of the antagonistic *N*-(cyclopropylmethyl) side chain and a 14β-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 14β-PhCH$_2$ and 14β-Pr derivatives turned out to be orally active antagonists and LH inducers, whereas 14β-Me- and 14β-Et-substituted compounds were orally inactive, although being potent antagonists upon intravenous application. Based on our finding that μ-antagonists with little $\varkappa$-affinity such as **12** and **11b**[5] showed no LH stimulation, we conclude that a combination of both μ- and $\varkappa$-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 (OFI 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 3*H*-naloxone and (−)-3*H*-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 Me_4Si (= 0 ppm). Mass spectra: *AEI MS 30* or *MAT 212* under EI or FAB conditions. Microanalyses of crystalline compounds were within ±0.4% of theoretical values.

2.2. *Exper. A: 17-(Cyclopropylmethyl)-4,5α-epoxy-3,6α-dimethoxy-6β,14β-(2-phenyl-1-thiaethane-1,2-diyl)-morphinane* (**2d**). *N*-(Cyclopropylmethyl)northebaine [6] (**1**; 40.4 g; 0.115 mol) and *S*-benzyl phenylmethanethiosulfinate [27] (21 g, 0.08 mol) were refluxed for 1 h in toluene (750 ml). The mixture was evaporated, mixed with H_2O, and extracted with Et_2O (3 ×). After drying (Na_2SO_4) and evaporation, recrystallization from Et_2O yielded **2d** (40.2 g, 74%) as white crystals. M.p. 149–150°. ^{1}H-NMR ($CDCl_3$, 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*, CH_2N, H_{ax}–C(10)); 3.05–3.15 (*m*, H–C(9), H_{eq}–C(10), H_{eq}–C(16)); 3.69 (*s*, CH_3O); 3.80 (*s*, CH_3O); 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-5β,14β-(1-thiapropane-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/Et_2O, and dried: **3b**·HBr (39.5 g, 83%). M.p. 256–258°. ^{1}H-NMR ($CDCl_3$, 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, CH_3); 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), CH_2N); 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*, CH_3O); 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)-14β-(1-mercaptoethyl)-3-methoxymorphinan-4,6-diol* (**4b**). Li (4.3 g, 0.62 mol) was dissolved in liq. NH_3 (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 NH_4Cl, NH_3 distilled off, and the residue taken up in H_2O and extracted with Et_2O (3 ×). Drying (Na_2SO_4), evaporation, and FC (AcOEt/hexanes 1:5) yielded **4b** (19.5 g, 87%; 6α/6β-mixture) as an oil.

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

2.5. *Exper. D: 17-(Cyclopropylmethyl)-14β-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 CH_2Cl_2, dried (Na_2SO_4), and evaporated: **5b** (11.5 g, 89%; 6α/6β-mixture) as a light red foam.

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

2.6. *Exper. E: 14β-Benzyl-17-(cyclopropylmethyl)-4-hydroxy-3-methoxymorphinan-6-one* (**6d**). Oxalyl chloride (11.2 ml, 0.123 mol) was added at −60° to CH_2Cl_2 (1.08 l) and mixed with DMSO (18.4 ml, 0.26 mol) in CH_2Cl_2 (250 ml). At −78°, **5d** (51.2 g, 0.118 mol) in CH_2Cl_2 (235 ml) was added, and after 15 min at −55°, Et_3N (77 ml, 0.55 mol) was introduced and the mixture warmed up to −10°. H_2O was added and the mixture extracted with CH_2Cl_2 (2 ×). After drying (Na_2SO_4), 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). ^{1}H-NMR ($CDCl_3/D_2O$, 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*, CH_2(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_b–C(22)); 3.82 (*s*, CH_3O); 4.01 (*d*, *J* = 12, H_a–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)-4,5α-epoxy-14β-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 Br_2 (19 g, 119 mmol) in AcOH (200 ml). After 90 min, the mixture was evaporated, taken up in CH_2Cl_2 (1 l), and poured under stirring and cooling into 1N NaOH (300 ml). The org. phase was washed with H_2O and a little 10% tartaric acic (to pH 7), dried (Na_2SO_4), and evaporated. The residue was dissolved in AcOH (170 ml) and H_2O (130 ml) and hydrogenated over Pd/C (3g) for 15 h at r.t. The mixture was filtered, evaporated, taken up in ice/2N Na_2CO_3, and extracted with CH_2Cl_2 (3 ×). Drying (Na_2SO_4) 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°. ^{1}H-NMR ($CDCl_3$, 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: 14β-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 H_2O and extracted with Et_2O (3 ×), 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). ^{1}H-NMR ($CDCl_3$, 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*, CH_2(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: 14β-Benzyl-17-(cyclopropylmethyl)-3-methoxy-4-phenoxymorphinan-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 K_2CO_3 (12.2 g, 87 mmol) and Venus-Cu (3 g) were added. The mixture was refluxed for 17 h (→ dark), then poured on ice/H_2O and extracted with Et_2O (3 ×). After drying (Na_2SO_4), 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: 14β-Benzyl-17-(cyclopropylmethyl)-3-methoxymorphinan-6-one* (**8d**). In a H_2O 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 Na_2CO_3 (1 l) was added and the mixture extracted with benzene (2 ×). After drying (Na_2SO_4), 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 NH_3 (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 NH_4Cl was added, NH_3 evaporated, and the residue taken up in H_2O and extracted with Et_2O (3 ×). The Et_2O phases were washed with 1N NaOH (2 ×) and H_2O (1 ×), dried (Na_2SO_4), 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: 14β-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 Et_2O, dried (Na_2SO_4), and evaporated. The resulting foam was dissolved in acetone/MeOH/HCl and warmed to 45° for 10 min, evaporated, taken up in 2N NH_3, and extracted with CH_2Cl_2 (3 ×). The resulting foam was purified by FC (AcOEt/hexanes 1:8): **6d** (2.3 g, 25%) as colourless crystals.

2.12. *Exper. K: 14β-Benzyl-17-(cyclopropylmethyl)-3-hydroxymorphinan* (**9d**[3]). A mixture of **9d**[4] (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/H_2O conc. NH_3 and extracted with Et_2O (3 ×). After drying (Na_2SO_4), evaporation, and purification by FC (CH_2Cl_2/MeOH/conc. NH_3 98:2:0.2), the org. phase yielded 1.9 g of olefinic intermediate as a white foam. This foam was dissolved in AcOH/H_2O (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/H_2O, made basic with conc. NH_3, extracted with Et_2O (3 ×), and purified by FC (AcOEt/hexanes 1:8 to 1:2): **9d**[3] (1.0 g, 48%) as colourless oil. M.p. of **9d**[3]·HCl > 280° (acetone/Et_2O). ^{1}H-NMR ($CDCl_3$, 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, H–C(1)); 7.15–8.0 (*m*, 5 H). MS: 387 (M^+).

We thank *P. Candotti* and *I. Leupi* for their capable technical assistance in the synthetic work, *H. R. Loosli*, *L. Oberer*, *M. Ponelle*, and *T. Zardin* for the interpretation and measurement of ^{1}H-NMR spectra, and *C. Quiquerez* for the interpretation and measurement of MS. Thanks are also due to Dr. *H. Braunschweiger* for a generous sample of thebaine derivative **1**.

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