Recl. Trav. Chim. Pays-Bas **107**, 449–454 (1988) 0165-0513/88/06449-06$2.00

Diels–Alder reaction of 6-demethoxy-β-dihydrothebaine with methyl vinyl ketone using microwave heating; preparation and pharmacology* of 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol, a novel deoxygenated diprenorphine analogue (chemistry of opium alkaloids, part XXV**)

J. T. M. Linders, J. P. Kokje, M. Overhand, T. S. Lie and L. Maat

Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

(Received February 4th, 1988)

Abstract. *Diels–Alder* reaction of 6-demethoxy-β-dihydrothebaine **6** with methyl vinyl ketone (3-buten-2-one) yielded, in a 3:2 ratio, (+)-7β-acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol (**7**) and the novel (+)-8β-acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol (**8**). Performing the reaction in a microwave oven resulted in a faster and cleaner reaction. ^{1}H NMR and mass spectra of **8** were studied and the structure was finally established by single-crystal X-ray analysis of its 4-*O*-phenyl ether **13**. In contrast to thebaine and 6-demethoxythebaine, the cycloaddition reaction of 6-demethoxy-β-dihydrothebaine with methyl vinyl ketone occurred at the α-face of the diene system.

Ullmann reaction of **7** with bromobenzene, followed by Grignard reaction with methylmagnesium bromide and removal of the phenoxyl group using sodium in liquid ammonia, afforded the tertiary alcohol **11**. *O*-Demethylation of **11** by potassium hydroxide in boiling glycol, using microwave heating, afforded (+)-3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol **12**. The structure of **12** was confirmed by ^{1}H NMR and single-crystal X-ray analysis. Compound **12** showed morphine-like activity in the PPQ assay.

Introduction

Diels–Alder reaction of 4,5α-epoxymorphinan-6,8-dienes with mono-substituted ethenes may afford, in principle, eight isomeric adducts. This was first observed by *Schöpf* in 1938[1]. A major breakthrough came in the early sixties when *Bentley* and *Hardy*[2-3] reported analgesics of extraordinary potency derived from 6α,14α-ethenoisomorphinans[4] (Scheme 1). The 7α-substituted isomer was the major product of the *Diels–Alder* reaction of thebaine (**1**) with unsymmetrical dienophiles such as acrylates or methyl vinyl ketone. Usually, a small amount of the 7β-substituted isomer accompanied the main product.

Only recently, 4,5α-epoxymorphinan-6,8-dienes other than thebaine have become available. The *Diels-Alder* reaction of 6-demethoxythebaine (**2**) gave the 7α-substituted 6α,14α-ethenoisomorphinan as the main product[5-7], together with 12% of the 8α-substituted derivative, whereas 6-deoxythebaine (**3**) gave a 96:3:1 ratio of the 7α-, 8α- and 7β-substituted 6α,14α-ethenoisomorphinans, together with a trace (0.1%) of the 8β-substituted 6β,14β-ethenomorphinan[8] (Scheme 1).

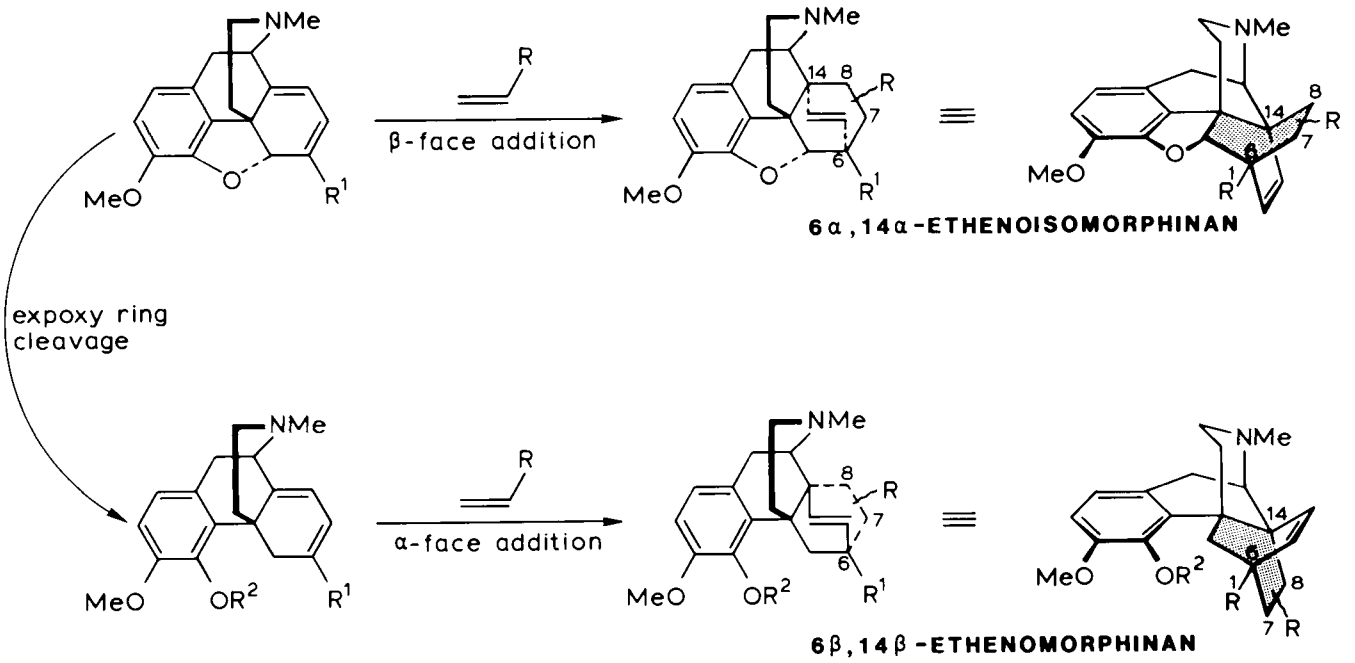
With a decreasing electronic influence at C-6, obviously the effect of the two alkyl substituents (C-9 and C-13) attached to C-14 becomes more important; this results in an increasing ratio of the 8α/7α isomers. The fact that the 7α-isomer remains the major product, even in the case of 6-demethoxythebaine, strongly indicates that stereochemical control dominates over electronic effects.

In contrast to the above mentioned *Diels–Alder* reaction of 4,5α-epoxymorphinan-6,8-dienes, the cycloaddition of dienophiles to morphinan-6,8-dienes *lacking the epoxy bridge* occurs exclusively from the other side, *i.e.* at the α-face of the diene system, yielding the 6β,14β-ethenomorphinans (Scheme 1). *Ghosh* et al.[9] reported on the *Diels-Alder* reaction of the 4-*O*-phenyl ether of β-dihydrothebaine (**5**) with methyl vinyl ketone and obtained the 7β-acetyl-6β,14β-ethenomorphinan. Simultaneously, we independently obtained similar results in preliminary experiments using a mixture of 6-demethoxy-β-dihydrothebaine (**6**) and its 5,8-diene isomer as starting material[7].

We now report on the *Diels–Alder* reaction of methyl vinyl

* Dr. *A. E. Jacobson*, National Institutes of Health, Bethesda, Md, U.S.A.

** Part XXIV: *R. A. van Gurp, T. S. Lie, C. Mense* and *L. Maat*, Bull. Soc. Chim. Belg. **96**, 325 (1987).



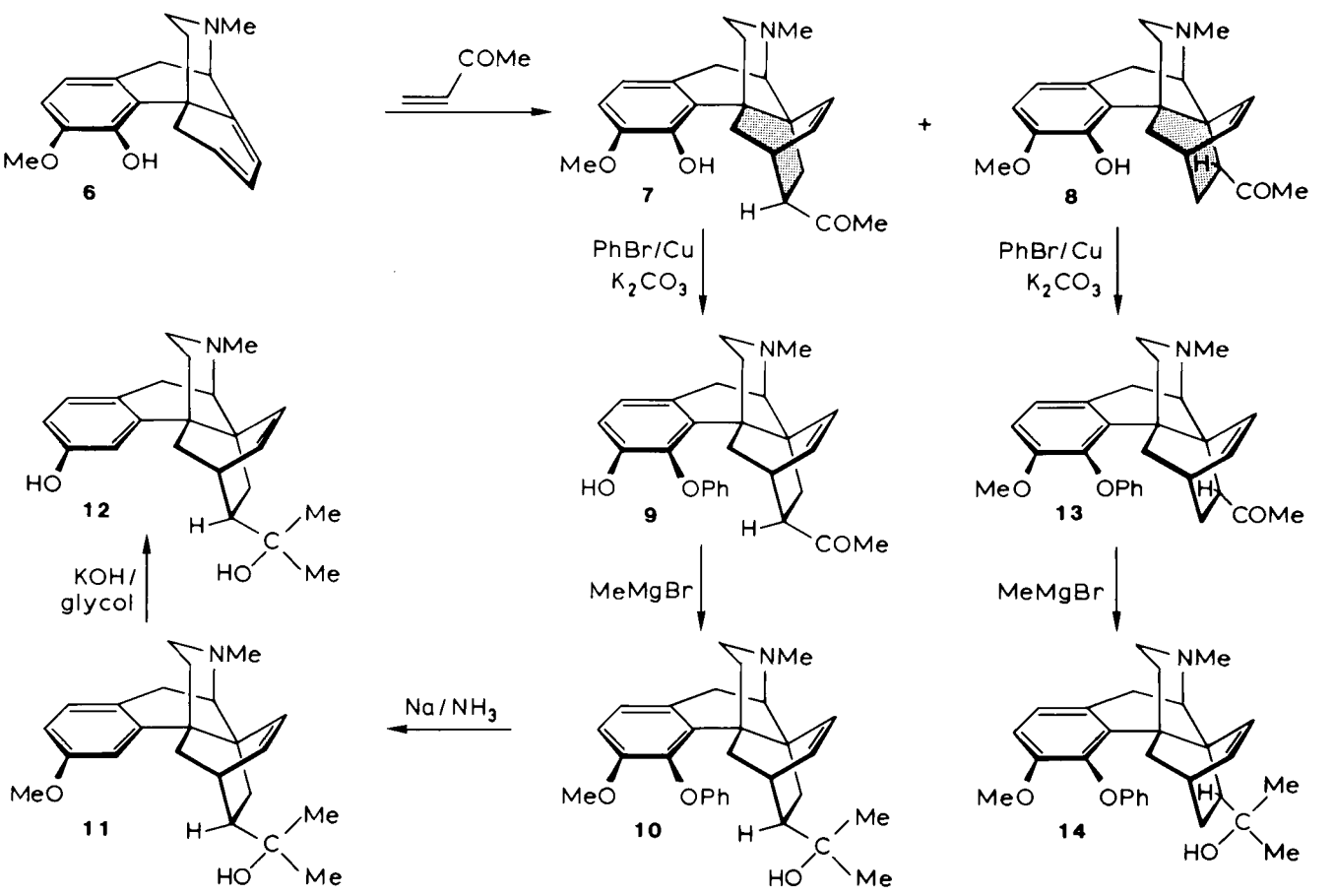
Scheme 1. Two ways of cycloaddition to morphinan-6,8-dienes.

ketone (3-buten-2-one) with 6-demethoxy-β-dihydrothebaine, for which we have developed a convenient synthesis[10]. The 7β-substituted adduct **7** thus obtained was converted into 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**12**), a novel diprenorphine analogue, for which we here present the first pharmacological results.

Results and discussion

Diels–Alder *reaction of 6-demethoxy-β-dihydrothebaine*

Heating 6-demethoxy-β-dihydrothebaine (**6**)[10] in an excess of methyl vinyl ketone under reflux for 60 h yielded two adducts, in a ratio of 3:2, according to HPLC (Scheme 2).



Scheme 2. Diels–Alder *reaction of 6-demethoxy-β-dihydrothebaine* (**6**) *with methyl vinyl ketone; conversion of adducts* **7** *and* **8** *into carbinols* **12** *and* **14**, *respectively.*

Table I Chemical shifts (ppm, $CDCl_3$) of the vinylic protons of some 6α,14α-ethenoisomorphinans and 6β,14β-ethenomorphinans.

Substitution pattern						Shifts		
4,5α	6,14	4	6	7	8	H-18	H-19	Ref.
-O-	α		OMe	α-NO_2		5.88–5.22		16
-O-	α		OMe	α-COMe		5.85	5.54	15
-O-	α		Me	α-COMe		5.36	5.60	8
-O-	α		H	α-COMe		5.60	5.54	6
-O-	β		H		β-NO_2	6.32	6.46	14
-O-	β		Me		β-COMe	6.75	5.62	8
	β	OPh	OMe	β-COMe		6.36	6.00	9
	β	OH	H	β-COMe		6.08	6.40	7
	β	OH	H		β-COMe	6.26	6.50	[a]
	β	OPh	H	β-COMe		6.00	6.40	[a]
	β	OPh	H		β-COMe	6.20	6.50	[a]

[a] This work.

In preliminary experiments[7], where **6** was only available as a mixture with its non-conjugated 5,8-diene isomer[7,10], the main product (**7**) could be isolated by column chromatography. The structure of the compound was elucidated by single-crystal X-ray analysis[11] and was proved to be the 7β-acetyl-6β,14β-ethenomorphinan **7**. This implies that the cycloaddition takes place at the α-side of the diene system. The *Diels–Alder* reaction performed under conventional conditions caused extensive polymerization of the dienophile, which made the work-up and the isolation of the adducts cumbersome. A dramatic improvement was achieved when the cycloaddition was carried out using a modified microwave oven. Recently, the use of microwave heating in organic synthesis has been reported[12,13]. The reactions described were carried out in closed vessels which resulted in high reaction pressure and temperature. In our set-up, we work under atmospheric conditions. Surprisingly, the reaction was complete within 24 h with substantially less formation of polymeric material, although the reaction temperature must have been similar to that in our earlier experiments[7]. The usual work-up procedure involving acid–base extraction gave the pure adducts **7** and **8** after selective crystallization.

Structure elucidation of the new addition product **8** met with difficulties. In the ^{1}H NMR spectrum, most of the signals could be assigned. From the shifts of the vinylic protons H-18 and H-19 at δ 6.26 and δ 6.50, respectively, it may be concluded that the etheno bridge is at the β-face of the molecule, as in adduct **7**. In the ^{1}H NMR spectra of other 6β,14β-ethenomorphinans[7-9,14], the vinylic protons are also found in this region, whereas these protons in the 6α,14α-ethenoisomorphinans are found below δ 6 (Table I). For a series of 22 compounds of the 6-methoxy-6α,14α--ethenoisomorphinan type, the signals of H-18 and H-19 are to be found at δ 5.91 (± 0.08) and δ 5.48 (± 0.06)[15], respectively. The downfield shift of the vinylic protons can be attributed to the deshielding effect of the aromatic nucleus. However, detailed ^{1}H NMR experiments, including solvent-induced shift, 2D-COSY and irradiation techniques, as well as ^{13}C NMR, did not result in an unequivocal assignment of the acetyl group. The signals of the protons at C-7 and C-8 coincide with those of the acetyl and *N*-methyl groups.

Mass spectrometry showed the expected molecular ion at *m/z* 353. The presence of a fragment *m/z* 57 (C_3H_5O) can be explained by a McLafferty rearrangement of the acetyl group. Molecular models show that this rearrangement can only occur in two 6β,14β-ethenomorphinans, *viz.* 7α- and 8β-acetyl, and in two 6α,14α-ethenoisomorphinans. However, the latter two can be ruled out on the basis of the NMR data.

From these spectral data, together with the application of the *Diels–Alder "endo"* rule[17], we tentatively assigned the 8β-acetyl-6β,14β-ethenomorphinan structure to amorphous **8**.

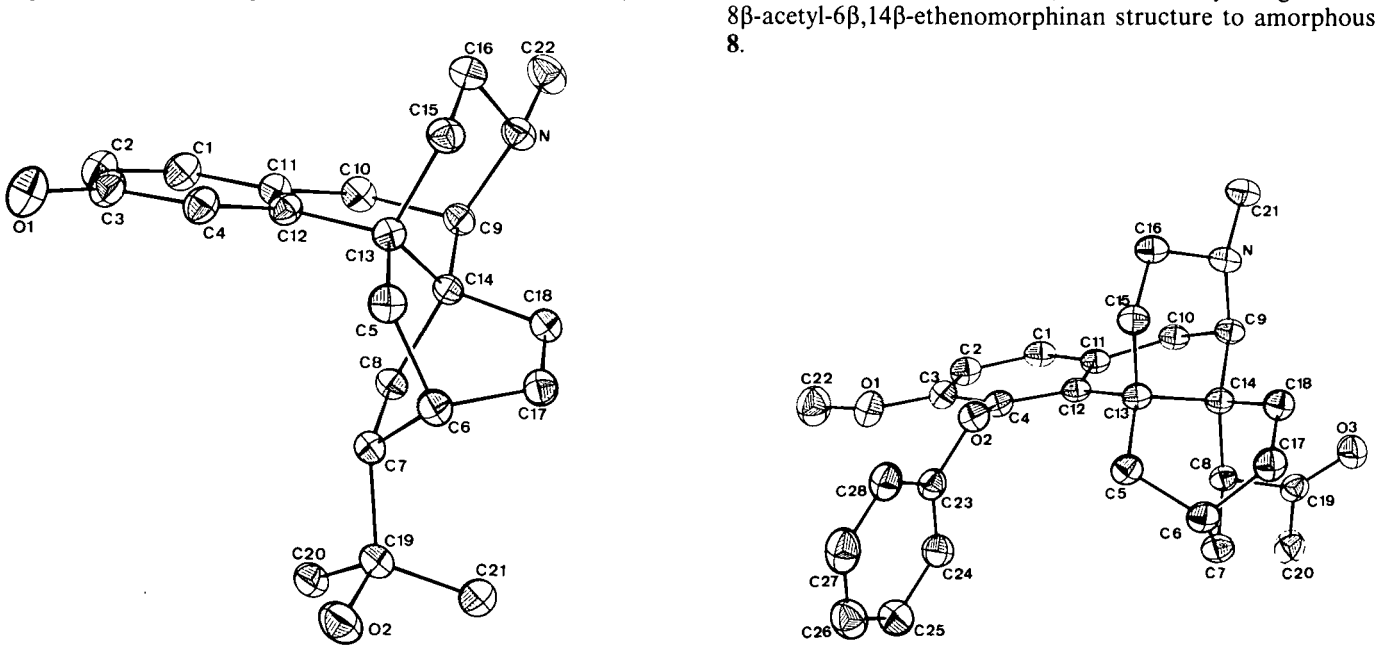


Fig. 1. Orientation of the 7β- and 8β-substituents of the ethenomorphinans **12** *(l) and* **13** *(r) from ORTEP drawings.*

In order to obtain final proof by single-crystal X-ray analysis, a crystalline derivative of **8** was required. Therefore, **8** was converted by an Ullmann reaction with bromobenzene into the 4-*O*-phenyl ether derivative **13** which readily crystallized from diethyl ether. The X-ray analysis[18] showed the compound to be the expected 8β-acetyl--3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan **13**, as depicted in Fig. 1. We may conclude that the *Diels–Alder* reaction of **6** with methyl vinyl ketone affords the 7β- and 8β-acetyl substituted 6β,14β-ethenomorphinans in a 3:2 ratio. Protection of the 4-hydroxyl group and *Diels–Alder* silica catalysis, as applied to β-dihydrothebaine (**4**)[9], are not required in this particular case in order to obtain satisfactory yields of the cycloadducts.

With respect to the site selectivity of the *Diels–Alder* reaction of 6-demethoxymorphinan-6,8-dienes, we may compare the cycloaddition with that of methyl vinyl ketone to 1-methyl-1,3-cyclohexadiene, which gave 2-acetyl--1-methylbicyclo[2.2.2]oct-5-ene as a 7:1 mixture of its epimers (90%)[19] (Scheme 3). Apparently, the methyl group has a strong directing effect on the *Diels–Alder* reaction. Both 6-demethoxythebaine and 6-demethoxy-β-dihydrothebaine can also be considered as substituted 1-alkyl--1,3-cyclohexadienes. Based on the above mentioned results, the cycloaddition reaction with monosubstituted dienophiles is expected to give the 8-substituted etheno(iso)-morphinan as the main product.

However, in the case of 6-demethoxythebaine (**2**), there is a preference for the formation of 7-substituted 6α,14α--ethenoisomorphinans (88%)[20]. The influence on the course of the cycloaddition, caused by the morphinan skeleton, must be mainly of steric origin, since electronic effects of substituents connected via a C atom (σ bond) to a diene system (*e.g.* the epoxy bridge) are negligible.

In the case of 6-demethoxy-β-dihydrothebaine (**6**), which lacks the epoxy bridge, the 7- and 8-substituted adducts are formed in a ratio of 3:2, indicating that steric factors also govern the cycloaddition in this compound. Remarkably, opening of the epoxy ring results in *Diels–Alder* reaction from the other side of the diene system, compared with 4,5α-epoxymorphinan-6,8-dienes. With the information at hand it is only possible to speculate as to the course of the cycloaddition; this reaction will be the subject of further study.

Preparation of 3-hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**12**)

The target molecule **12**, reminiscent both of diprenorphine and of compounds previously prepared by us[7,21], was chosen for pharmacological testing. To prepare this compound, we followed the reaction pathway depicted in Scheme 2. Dehydroxylation of **7** was achieved using the procedure of *Sawa* et al.[22]. Reaction of the 4-hydroxyl group of **7** with bromobenzene in boiling pyridine in the presence of potassium carbonate and copper powder gave the crystalline 4-phenyl ether derivative **9**. At this stage, the acetyl group was converted into the desired tertiary alcohol by means of a Grignard reaction with methylmagnesium bromide because of its expected susceptibility in liquid ammonia. The phenoxyl group was then easily removed by sodium in liquid ammonia, affording **11**.

Finally, *O*-demethylation of **11**, using potassium hydroxide in glycol[2] with a small amount of water[7] and applying microwave heating, gave the desired phenolic compound **12**. First attempts at this demethylation using boron tribromide resulted in a complex mixture, as previously experienced in the case of the 4,5α-epoxy adducts[7].

The structure of **12** was definitively proven by single-crystal X-ray analysis[23] to be 3-hydroxy-α,α,17-trimethyl-6β,14β--ethenomorphinan-7β-methanol (Fig. 1), excluding a possible epimerization of the acetyl side-chain during the Ullmann and Grignard reactions.

Initial attempts to dehydroxylate **7** involving heterogeneously catalyzed hydrogenolysis were unsuccessful. Hydrogenolysis of the 5-phenyl-1-tetrazolyl ether using hydrogen and palladium on charcoal[24] or hydrogen transfer methods[25] resulted in reduction of the etheno bridge, while forcing conditions[26] under high pressure only led to decomposition. An attempt to hydrogenolyze the mesyl ester[27] of **7** also resulted in reduction of the double bond.

The Grignard reaction of the 8β-acetyl compound **13** with methylmagnesium bromide was laborious. A competitive side-reaction[8] seems to be the deprotonation of the acetyl group by the Grignard reagent. Hydrolysis of the reaction product gives a mixture of the starting material and some alcohol **14**. Repeating this procedure six times, finally, gave an acceptable yield (64%) of alcohol **14**.

Pharmacology*

Compound **12** appears to show activity in only one of the biological assays (sc injection in mice). In the PPQ (paraphenylquinone stretching) assay it is morphine-like. In the tail-flick test at 1.0, 10.0 and 30.0 mg/kg the compound is inactive as it is in the mouse hot-plate assay.

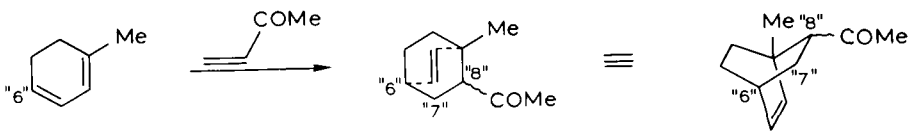
Since it has been previously noted that the PPQ assay is less discriminating with respect to the opioid-like activity, the compound will be examined further at the receptor level.

Experimental

Mass spectra were measured by Dr. *B. van de Graaf*, Mr. *H. Buurmans* and Mrs. *A. H. Knol–Kalkman* using a Varian MAT 311A mass spectrometer. ^{1}H NMR spectra were measured using a Varian T-60 spectrometer. The 200-MHz spectra were obtained using a Nicolet NT-200 WB, operated by Dr. *J. A. Peters* and Dr. *A. Sinnema*. All spectra were recorded in $CDCl_3$ as solvent with tetramethylsilane as reference. Rotations were measured using a Perkin-Elmer P141 polarimeter in chloroform/ethanol 9:1 as solvent.

Reactions were monitored by TLC on deactivated silica (0.25 mm, Merck F_{254}; eluent: dichloromethane/methanol/25% ammonia 85/15/0.5). The compounds were detected with UV (254 nm), iodine vapour and, in the case of phenolic compounds, with 2,6-dibromoquinone 4-chloroimide[28]. Melting points are uncorrected. Analytical HPLC was performed using a Waters

* Dr. *A. E. Jacobson*, National Institutes of Health, Bethesda, Md, U.S.A.



Scheme 3. Diels–Alder *reaction of 1-methyl-1,3-cyclohexadiene with methyl vinyl ketone.*

M-6000 pump on a reversed-phase column (8 × 100 mm, Nucleosil C_{18} or NovaPak, 10 μm, 30°C), using mixtures of methanol/water/trifluoroacetic acid as eluent, with detection on an ERMA RI-detector ERC-7510 or a Pye LC3 variable wave length detector at 240–250 nm. IR spectra were obtained from KBr discs using a Beckman IR 4210 spectrophotometer.

For microwave heating, we used a Sharp R-4060(w), 400 W, 2450 MHz microwave oven in the back wall of which a hole was bored for connection with a reflux condensor which was wrapped in copper wire gauze. After every 15 min of heating, the oven was switched off for 15 min to prevent overheating.

(+)-7β-Acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol (**7**) *and (+)-8β-acetyl-3-methoxy-17-methyl-6β,14β-ethenomorphinan-4-ol* (**8**)

6-Demethoxy-β-dihydrothebaine (**6**)[10] (10.2 g, 35 mmol) was boiled under reflux in 125 ml of freshly distilled methyl vinyl ketone using microwave heating (see introduction, experimental section). After 24 h, the mixture was evaporated *in vacuo*. The residue was dissolved in methanol and evaporated to dryness. The solid material (29.3 g) was dissolved in 300 ml of 0.5 *N* sulfuric acid and extracted with chloroform (5 × 75 ml). The organic layers were washed with 0.5 *N* sulfuric acid. The combined aqueous fractions were rendered alkaline with 4 *N* ammonia (pH 9–10) and extracted with chloroform (3 × 100 ml). The chloroform extract was washed with water (2 × 50 ml) and dried (Na_2SO_4) and the solvent was removed *in vacuo* (coevaporation with methanol), giving 9.25 g of solid material. Crystallization from methanol/diethyl ether gave 2.71 g (7.7 mmol, 22%) of the 7β-acetyl adduct **7** as white needles. M.p. 202°C (ref. 7: m.p. 204–205°C); $[\alpha]_D^{25}$ 100° (*c* 1) [ref. 7: $[\alpha]_D^{25}$ 95° (*c* 1.1)]. MS: *m/z* 353 (M^+, 100), 310 (31), 282 (15), 190 (24), 44 (47). ^{1}H NMR: ref. 7. IR: ν_{max}^{KBr} 3350 (OH), 1700 (C=O) cm^{-1}.

Evaporation of the mother liquor and repeated crystallization from methanol/diethyl ether gave 1.27 g (3.6 mmol, 10%) of the 8β-acetyl adduct **8** as a white amorphous material. M.p. 172–173°C; $[\alpha]_D^{25}$ 102° (*c* 1.2). MS: *m/z* 353 (M^+, 100), 310 (33), 282 (47), 190 (33), 110 (45), 57 (69). ^{1}H NMR: δ 1.20 (m, 1H, H-15′), 1.68 (dd, 1H, H-5, *J*(5,6) 2.3 Hz, *J*(5,5′) − 13.7 Hz), 1.80 (m, 1H, H-16′), 1.90 (m, 2H, H-8 + H-15), 1.97 (s, 3H, $COCH_3$), 2.00 (m, 1H, H-5), 2.30 (m, 1H, H-7′), 2.35 (s, 3H, NCH_3), 2.56 (dd, 1H, H-10′, *J*(1,10′) 1 Hz, *J*(10,10′) − 19.0 Hz), 2.60 (m, 1H, H-6), 2.97 (dd, 1H, H-10, *J*(9,10) 5.0 Hz), 3.00 (m, 1H, H-7), 3.19 (d, 1H, H-9), 3.87 (s, 3H, OCH_3), 5.87 (bs, 1H, OH), 6.26 (dd, 1H, H-18, *J*(18,19) 8.2 Hz, *J*(6,18) 6.5 Hz), 6.50 (d, 1H, H-19), 6.62 (d, 1H, H-1, *J*(1,2) 8.3 Hz), 6.71 (d, 1H, H-2). IR: ν_{max}^{KBr} 3360 (OH), 1700 (C=O) cm^{-1}.

(+)-7β-Acetyl-3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan (**9**)

The 7β-acetyl compound **7** (7.01 g, 19.9 mmol) was dissolved in 100 ml of pyridine (dried over KOH). Bromobenzene (4.0 g, 25.6 mmol), copper powder (4 g, 63 mmol) and solid anhydrous potassium carbonate (4 g, 29 mmol) were added and the mixture was boiled under reflux in a nitrogen atmosphere for 100 h.

The mixture was filtered over hyflo and the residue was washed with warm pyridine (3 × 15 ml). The filtrate was evaporated *in vacuo* and the oily residue was dissolved in 300 ml of toluene. This solution was washed with ammonia (3 × 75 ml) and water (2 × 50 ml). After drying (Na_2SO_4), the solvent was removed *in vacuo* and the residue was dissolved in 300 ml of diethyl ether. A fine precipitate was removed by filtration. After evaporation of the ether, the residue was taken up in 750 ml of hexane. Filtration and removal of the solvent gave 7.79 g of an off-white foam. Crystallization from 400 ml of hexane gave 4.15 g (9.7 mmol, 49%) of compound **9**. M.p. 158°C; $[\alpha]_D^{25}$ 93° (*c* 1). MS: *m/z* 429 (M^+, 100), 386 (25), 358 (10), 266 (20). ^{1}H NMR: δ 2.05 (s, 3H, $COCH_3$), 2.35 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 6.00 (dd, 1H, H-18, *J*(18,19) 8 Hz), *J*(6,18) 6 Hz), 6.40 (d, 1H, H-19), 6.70–7.40 (m, 7H, Ar–H). IR: ν_{max}^{KBr} 1705 (C=O) cm^{-1}.

(+)-3-Methoxy-α,α,17-trimethyl-4-phenoxy-6β,14β-ethenomorphinan-7β-methanol (**10**)

To a boiling mixture of 150 ml of anhydrous diethyl ether and 4 ml of a 3-M solution of methylmagnesium bromide in diethyl ether (12 mmol), a solution of the 7β adduct **9** (3.82 g, 8.9 mmol) in 150 ml of diethyl ether was added dropwise (20 min). After completion of the addition, an additional amount of 3 M methylmagnesium bromide solution (0.4 ml, 1.2 mmol) was added to the mixture. After 10 min, all starting material had disappeared (TLC), the oil bath was removed and a solution of ammonium chloride (12 g) in 200 ml of water was added cautiously. The layers were separated and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic fractions were washed with water (2 × 50 ml), dried (Na_2SO_4) and evaporated to dryness, yielding 3.82 g (8.6 mmol, 96%) of the title compound **10** as a white foam, pure according to TLC and HPLC. $[\alpha]_D^{25}$ 72° (*c* 0.7). MS: *m/z* 445 (M^+, 100), 386 (32), 358 (20), 266 (35). ^{1}H NMR: δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.32 (s, 3H, NCH_3), 6.20 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 6 Hz), 6.50 (d, 1H, H-19), 6.70–7.40 (m, 7H, Ar–H). IR: ν_{max}^{KBr} 3560 (OH) cm^{-1}.

(+)-3-Methoxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**11**)

A solution of **10** (3.72 g, 8.4 mmol) in 150 ml of diethyl ether (dried over molecular sieve 4 Å) was added over 30 min to a solution of 1 g (44 mmol) of sodium in 200 ml of liquid ammonia at −58°C[29]. After 10 min, the reaction was complete (TLC), solid ammonium chloride and ethanol were added and the mixture was warmed to room temperature. The solvents were evaporated *in vacuo*. The residue was taken up into 100 ml of water and rendered alkaline with 2 *N* KOH solution (100 ml) to pH 9–10. This solution was extracted with dichloromethane (75 ml and 2 × 30 ml). The combined organic layers were washed with 2 *N* KOH (2 × 50 ml) and water (2 × 50 ml) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave 3.00 g (8.4 mmol, 100%) of pure (TLC, HPLC) **11** as a white foam. $[\alpha]_D^{25}$ 54° (*c* 1). MS: *m/z* 353 (M^+, 100), 338 (19), 336 (14), 294 (28), 266 (12), 221 (15), 209 (20), 195 (11), 174 (14). ^{1}H NMR: δ 0.97 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.38 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 6.21 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 6 Hz), 6.50 (d, 1H, H-19), 6.74–7.08 (m, 3H, Ar–H). IR: ν_{max}^{KBr} 3450 (OH) cm^{-1}.

(+)-3-Hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol (**12**)

A solution of compound **11** (2.32 g, 6.6 mmol) and potassium hydroxide (15 g) in a mixture of glycol (75 ml) and water (1 ml) was refluxed using microwave heating. After 5 h heating, 15 g of potassium hydroxide and 1 ml of water were added. The heating was continued for a further 5 h (complete conversion on TLC). After cooling to room temperature, the reaction mixture was diluted with 100 ml of water and extracted with dichloromethane (50 ml) to remove non-phenolic material. The aqueous layer was adjusted with concentrated hydrochloric acid to pH 7–8 and thoroughly extracted with dichloromethane (14 × 60 ml) and diethyl ether (5 × 70 ml). The combined organic layers where washed with water, dried (Na_2SO_4) and evaporated *in vacuo*, yielding 1.40 g (4.1 mmol, 63%) of pure (TLC) **12** as a white foam. Crystallization from hexane/diethyl ether gave 270 mg of the 3-hydroxy adduct **12** as white crystals, suitable for X-ray analysis. M.p. 184–186°C (dec.); $[\alpha]_D^{25}$ 55° (*c* 0.7). MS: *m/z* 339 (M^+, 100), 324 (18), 280 (29), 252 (12), 195 (19), 160 (14). ^{1}H NMR: δ 0.99 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.38 (s, 3H, NCH_3), 2.72 (dd, 1H, H-10, *J*(9,10) 5.5 Hz, *J*(10,10′) − 18 Hz), 2.77 (m, 1H, H-6), 2.92 (d, 1H, H-9), 3.06 (d, 1H, H-10′), 6.19 (dd, 1H, H-18, *J*(18,19) 8.1 Hz, *J*(6,18) 6.3 Hz), 6.50 (d, 1H, H-19), 6.58–6.94 (m, 3H, Ar–H). IR: ν_{max}^{KBr} 3300 (OH) cm^{-1}. X-ray analysis, ref. 23: $C_{22}H_{29}NO_2$, mol. wt. 339.5. Orthorhombic, $P2_12_12_1$, a = 7.810 (2), b = 14.152 (2), c = 16.705 (4) Å, V = 1846.4 Å^3, Z = 4, D_x = 1.23 g·cm^{-3}.

(+)-8β-Acetyl-3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan (**13**)

Bromobenzene (1.75 g, 11.2 mmol), copper powder (1.75, 27.8 mmol) and anhydrous, powdered potassium carbonate (1.75 g, 12.8 mmol) were added to a solution of the 8β-acetyl adduct **8** (2.88 g, 8.2 mmol) in pyridine (45 ml). After 50 h boiling, the reaction was complete. The mixture was cooled to room temperature, filtered and worked up as described for the 7β-acetyl adduct **9**. The treatment with hexane was repeated three times, yielding 1.97 g (4.6 mmol, 56%) of pure **13** after evaporation of the solvent. Crystalli-

zation from diethyl ether gave suitable crystals for X-ray analysis. M.p. 130–131°C; $[\alpha]_D^{25}$ 90° (*c* 1). MS: *m/z* 429 (M^+, 100), 386 (20), 358 (28), 266 C24). ^{1}H NMR: δ 1.96 (s, 3H, $COCH_3$), 2.33 (s, 3H, NCH_3), 3.62 (s, 3H, OCH_3), 6.20 (dd, 1H, H-18, *J*(18,19) 8 Hz, *J*(6,18) 6 Hz), 6.50 (d, 1H, H-19), 6.70–7.40 (m, 7H, Ar–H). IR: ν_{max}^{KBr} 1705 (C=O) cm^{-1}. X-ray analysis, ref. 18: $C_{28}H_{31}NO_3$, mol. wt. 429.6. Orthorhombic, $P2_12_12_1$, a = 11.899 (2), b = 15.511 (3), c = 20.543 (4) Å, V = 2292.3 Å^3, Z = 4, D_x = 1.25 g·cm^{-3}.

(+)-3-Methoxy-α,α,17-trimethyl-4-phenoxy-6β,14β-ethenomorphinan-8β-methanol (**14**)

A solution of **13** (1.65 g, 3.8 mmol) in 50 ml of anhydrous diethyl ether was added over 30 min to a boiling mixture of diethyl ether (100 ml) and a 3-M solution (2 ml, 6 mmol) of methylmagnesium bromide in diethyl ether. After the addition was complete, the excess of the Grignard reagent was destroyed with a saturated ammonium chloride solution, the layers were separated and the aqueous fraction was extracted with diethyl ether (2 × 25 ml). The combined ether fractions were dried (Na_2SO_4) and evaporated *in vacuo*. The residue, which consisted of a mixture of carbinol **14** and unreacted **13**, was redissolved in 50 ml of diethyl ether and again treated with methylmagnesium bromide solution (2 ml, 6 mmol). This procedure was repeated five times, finally giving 1.08 g (2.4 mmol, 64%) of **14**. M.p. 199–202°C (dec.); $[\alpha]_D^{25}$ 53° (*c* 1). MS: *m/z* 445 (M^+, 100), 430 (10), 386 (23), 358 (27),281 (12), 266 (19). ^{1}H NMR: δ 0.90 (m, 2H, H-15, H-15′), 1.04 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.11 (m, 1H, H-8), 1.60 (m, 2H, H-5 + H-5′), 1.90 (m, 1H, H-7), 2.00 (m, 2H, H-16 + H-16′), 2.20 (m, 1H, H-7′), 2.33 (s, 3H, NCH_3), 2.40 (m, 1H, H-6), 2.92 (dd, 1H, H-10, *J*(9,10) 5.8 Hz, *J*(10,10′) – 18.6 Hz), 3.38 (d, 1H, H-9), 3.64 (s, 3H, OCH_3), 3.66 (d, 1H, H-10′), 6.06 (dd, 1H, H-18, *J*(18,19) 8.1 Hz, *J*(6,18) 6.1 Hz), 6.34 (d, 1H, H-19), 6.68 (d, 1H, H-1, *J*(1,2) 8.6 Hz), 6.72 (d, 1H, H-2), 6.80–7.25 (m, 5H, PhO–). IR: ν_{max}^{KBr} 3400 (OH) cm^{-1}.

Acknowledgements

We are grateful to the Management of Diosynth, B.V., Apeldoorn, The Netherlands for the gift of chemicals. One of us (J.T.M.L.) wishes to express his gratitude for financial support from Diosynth, B.V. We thank the U.S.A. Committee on Problems of Drug Dependence, Inc. and Dr. *A. E. Jacobson*, Chairman, Drug Testing Program, for the results of the pharmacological studies. We thank Dr. *J. A. Peters* and Dr. *A. Sinnema* for interpretation of the 200-MHz ^{1}H NMR spectra and Dr. *B. van de Graaf* for interpretation of the mass spectra.

References

[1] *C. Schöpf, K. von Gottberg* and *W. Petri*, Lieb. Ann. Chem. **536**, 216 (1938).
[2] *K. W. Bentley* and *D. G. Hardy*, Proc. Chem. Soc. 220 (1963).
[3] *K. W. Bentley* in "The Alkaloids", Vol. XIII, Ed. *R. H. F. Manske*, Academic Press, New York, London, 1971, p. 75.
[4] See foot-note on nomenclature of etheno(iso)morphinans in Ref. 7.
[5] *P. R. Crabbendam, L. Maat* and *H. C. Beyerman*, Recl. Trav. Chim. Pays-Bas **100**, 293 (1981).
[6] *C. W. Hutchins, G. K. Cooper, S. Pürro* and *H. Rapoport*, J. Med. Chem. **24**, 773 (1981).
[7] *P. R. Crabbendam, T. S. Lie, J. T. M. Linders* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **103**, 296 (1984).
[8] *L. C. Knipmeyer* and *H. Rapoport*, J. Med. Chem. **28**, 461 (1985).
[9] *A. C. Ghosh, D. E. Portlock, H. C. Dalzell, C. Malmberg, P. Herlihy, R. K. Razdan, W. L. Duax* and *D. G. Smith*, J. Org. Chem. **48**, 4137 (1983).
[10] *J. T. M. Linders, R. J. O. Adriaansens, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **105**, 27 (1986).
[11] *H. van Koningsveld, L. Maat* and *T. S. Lie*, Acta Crystallogr. C**40**, 1082 (1984).
[12] *R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge* and *J. Rousell*, Tetrahedron Lett. **27**, 279 (1986).
[13] *R. J. Giguere, T. L. Bray, S. M. Duncan* and *G. Majetich*, Tetrahedron Lett. **27**, 4945 (1986).
[14] *M. A. Prazeres, J. A. Peters, J. T. M. Linders* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **105**, 554 (1986).
[15] *W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora* and *R. A. Hardy*, J. Am. Chem. Soc. **89**, 3322 (1967).
[16] *L. Maat, J. A. Peters* and *M. A. Prazeres*, Recl. Trav. Chim. Pays-Bas **104**, 205 (1985).
[17] *R. Gleiter* and *M. C. Böhm*, Pure Appl. Chem. **55**, 237 (1983).
[18] *H. van Koningsveld, J. C. Jansen, M. Overhand, L. Maat* and *T. S. Lie*, Acta Crystallogr. C**43**, 1773 (1987).
[19] *R. P. Gregson* and *R. N. Mirrington*, Aust. J. Chem. **29**, 2049 (1976).
[20] 8α-Acetyl-4,5α-epoxy-3-methoxy-6α,14α-ethenoisomorphinan could be isolated from the reaction mixture obtained from the *Diels–Alder* reaction of 6-demethoxythebaine with methyl vinyl ketone, after crystallization of the major 7α-acetyl adduct[7], by column chromatography followed by preparative TLC (multiple elution). The ^{1}H NMR spectrum was in accordance with the published, calculated spectrum[6]; *J. T. M. Linders, T. S. Lie* and *L. Maat*, to be published.
[21] 4,5α-Epoxy-α,α,17-trimethyl-6α,14α-ethenoisomorphinan-7α-methanol, *J. T. M. Linders, T. S. Lie* and *L. Maat*, to be published.
[22] *Y. K. Sawa, N. Tsuji* and *S. Maeda*, Tetrahedron **15**, 144 (1961).
[23] *H. van Koningsveld, J. C. Jansen, M. Overhand, T. S. Lie* and *L. Maat*, Acta Crystallogr. C**43**, 2384 (1987).
[24] *H. C. Beyerman, E. Buurman, T. S. Lie* and *L. Maat*, Recl. Trav. Chim. Pays-Bas **95**, 43 (1976).
[25] *B. J. Hussey, R. A. W. Johnstone* and *I. D. Entwistle*, Tetrahedron **38**, 3775 (1982).
[26] *J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson* and *A. Brossi*, J. Med. Chem. **22**, 256 (1979).
[27] *K. Clausz* and *H. Jensen*, Angew. Chem. **85**, 981 (1971).
[28] *E. Nürnberg*, Dtsch. Apoth. Ztg. **101**, 268 (1961).
[29] *H. C. Beyerman, F. F. van Leeuwen, T. S. Lie, L. Maat* and *C. Olieman*, Recl. Trav. Chim. Pays-Bas **95**, 238 (1976).