235. Structure-Activity Relationship of Oxygenated Morphinans. VII. 5-Methylated and 14-Hydroxy-substituted Agonists and Antagonists of the 4-Hydroxy- and 3,4-Dioxygenated 6-Morphinanone Series

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(28. VII. 82)

Summary

Several morphinanone agonists differently substituted at C(3), C(4), C(5) and C(14) and antagonists of the 4-hydroxy and 3,4-dimethoxy series were prepared by conventional chemistry. It was demonstrated that the oxygenation pattern in the bay-area, encompassing C(3) and C(4), is important. Alkylation at C(5) or hydroxylation at C(14) lowered the potency of the compounds. The most potent agonist was found to be the *N*-phenethyl-substituted ketone **27**, which was six times more potent than morphine in the hot-plate assay. The 3,4-methylenedioxy-substituted ketone **9** was about 20 times less potent than its 3,4-dimethoxy congener. An X-ray analysis of **9** and a representative agonist showed that the stereochemical features in the bay-area were similar and could not be used to explain this difference.

The chemistry and the biological properties of 6-morphinanones with narcotic agonist and antagonist properties have recently been reviewed [1]. It became apparent from this work that substituents which have the greatest effect on analgesic potency were located in the bay-area, encompassing C-atoms C(3) to C(6). The introduction of a 14-hydroxy group influenced the potency to a much lesser extent, and the change from a *N*-methyl to an *N*-allyl substitution afforded, as experienced in the morphinan family [2], compounds with narcotic antagonist properties. In order to further elaborate on the effect of changes at these locations, we considered it worthwhile to prepare morphinanones differently substituted at C(3)/C(4) and methylated at C(5) *(Scheme 1)*, some 14-hydroxy substituted analogs *(Scheme 2)*, and novel morphinanones with *N*-substituents known to introduce potent agonist or antagonistic effects *(Scheme 3)*.

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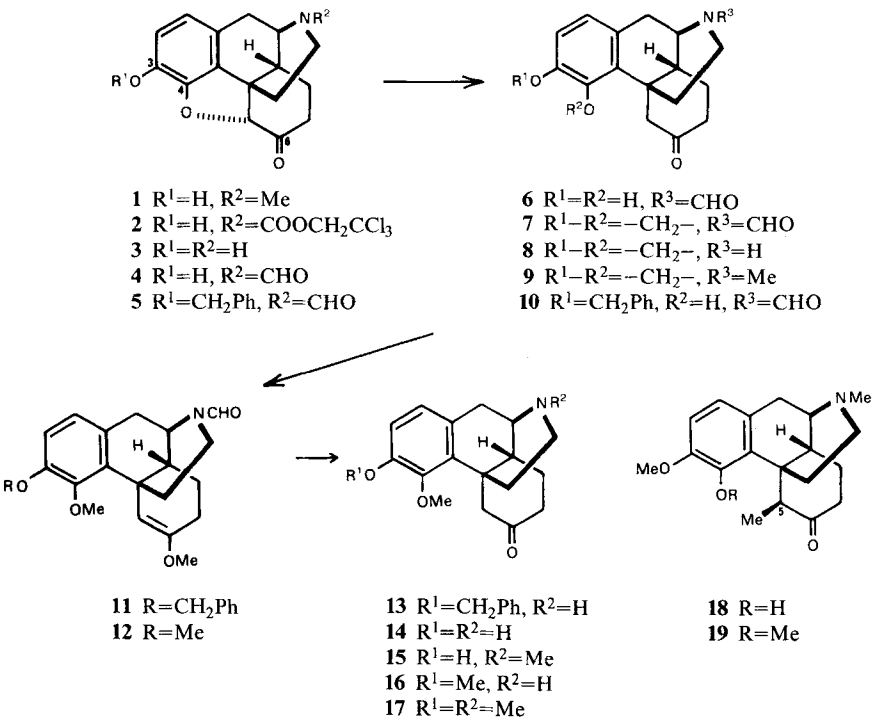
0018-019X/82/8/2394-11$01.00/0

Scheme 1



1 R^1=H, R^2=Me
2 R^1=H, R^2=$COOCH_2CCl_3$
3 R^1=R^2=H
4 R^1=H, R^2=CHO
5 R^1=CH_2Ph, R^2=CHO

6 R^1=R^2=H, R^3=CHO
7 R^1–R^2=–CH_2–, R^3=CHO
8 R^1–R^2=–CH_2–, R^3=H
9 R^1–R^2=–CH_2–, R^3=Me
10 R^1=CH_2Ph, R^2=H, R^3=CHO

11 R=CH_2Ph
12 R=Me

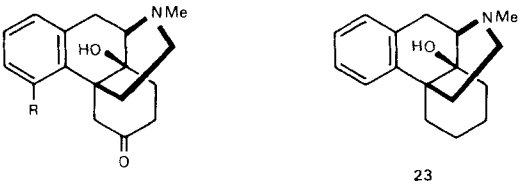
13 R^1=CH_2Ph, R^2=H
14 R^1=R^2=H
15 R^1=H, R^2=Me
16 R^1=Me, R^2=H
17 R^1=R^2=Me

18 R=H
19 R=Me

Chemistry. – The *N*-formyl-protected ketone **4**, prepared from the 7,8-dihydromorphinone (**1**) *via* **2** and **3** [3] by procedures elaborated in another series of morphinans [4], served as a starting material to prepare compounds **5**–**17** *(Scheme 1)*: reduction of **4** with $Zn/NH_4Cl/EtOH$ under reflux gave catechol **6**, which was methylenated with bromochloromethane to afford **7**. Hydrolysis of **7** afforded the secondary amine **8** and its *N*-methylation provided the required ketone **9**. The ^{1}H-NMR. spectrum of **8** and **9** showed the methylene protons of the methylenedioxy substituent as singlets at 5.88 and 5.90 ppm, suggesting that the CH_2-bridge was in solution out of the plane of the aromatic ring [5].

O-Methylation of **6** with methyl *p*-toluenesulfonate afforded the enol ether **12**, showing the vinylic proton at C(5) as a singlet at 5.45 ppm. Hydrolysis of **12** gave **16** which was converted into the known 3,4-dimethoxy ketone **17** by *N*-methylation [6]. The synthesis of the 'reverse' dihydrothebainone **15** (3-OH/4-OMe instead of 3-OMe/4-OH) was accomplished from the benzyl ether **5** *via* **10**, **11**, **13** and **14**, all obtained as well-characterized intermediates *(Scheme 1)*. It is interesting to note that the treatment of **5** with $Zn/NH_4Cl/EtOH$, used for the opening of the epoxy bridge, left the benzyloxy group intact. The ketone **19**, methylated at C(5), was prepared from the known phenol **18** [7] by *O*-methylation with phenyltrimethylammonium chloride.

Scheme 2



20 R = OH

21 R = O–(N-N, N-N, Ph)

22 R = H

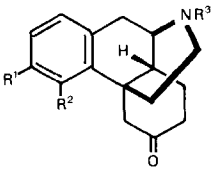
23

The second group of compounds *(Scheme 2)* were prepared from the known dihydroxy ketone **20** [8], which was 4-deoxygenated by catalytic reduction of its *N*-phenyltetrazolyl ether **21**, to afford the hydroxy ketone **22** with the unsubstituted aromatic ring. *Wolff-Kishner* reduction of **22** provided the morphinanol **23**. Both **22** and **23** are 14-OH analogs of well-characterized morphinans [9].

The third group of compounds *(Scheme 3)* included the *N*-allyl derivative **25** obtained from **24** by *N*-allylation, and the potential antagonist **26** of the dimethoxy series, prepared from the known ketone **16** [10] in the usual way [11], and the *N*-phenethyl-substituted ketone **27**.

X-Ray structure analysis of *9* and *28*. – A 20-fold difference in potency between morphinanones **17** and **28** on one hand and the methylenedioxy-substituted ketone **9** on the other hand in the hot-plate assay (see *Table*) was unexpected, and suggested that the stereochemical features of **9** and **28** be further explored by a single crystal X-ray analysis. It was hoped that such an investigation would complement the findings made in the ^{1}H-NMR. analysis of **9**, indicating that the CH_2-group of the five-membered ring might be out of the aromatic plane, and therefore that this ring might be much more available to ether cleavage and metabolic degradation.

Scheme 3



24 R^1=R^3=H, R^2=OH
25 R^1=H, R^2=OH, R^3=CH–CH=CH_2
26 R^1=R^2=OMe, R^3=CH_2–cyclopropyl
27 R^1=R^2=OMe, R^3=CH_2CH_2Ph
28 R^1=H, R^2=OMe, R^3=Me

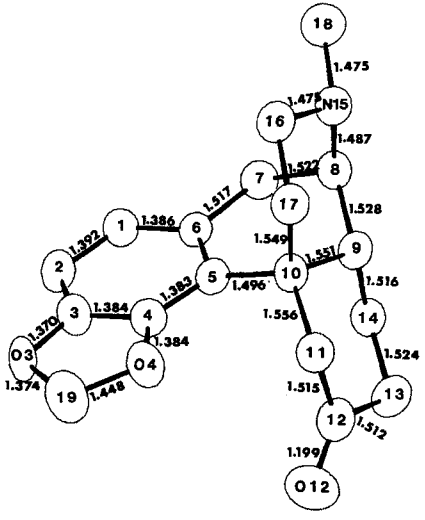


Fig. 1. *The X-ray diffraction structure of* **9** *showing the atomic numbering, bond lengths and thermal ellipsoids at a 50% -probability level* (Esd's for bond lengths are on the order of 0.005 A)

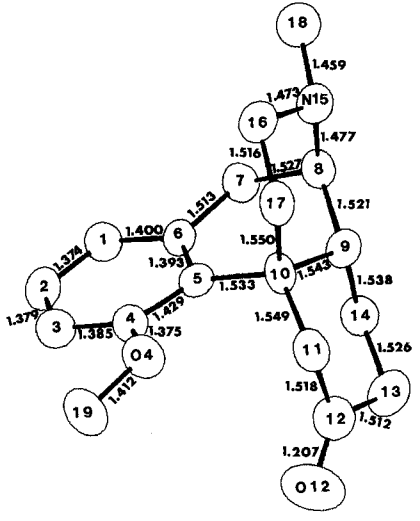


Fig. 2. *The X-ray diffraction structure of* **28** *showing the atomic numbering, bond lengths and thermal ellipsoids at a 50% -probability level* (Esd's for bond lengths are on the order of 0.003 A)

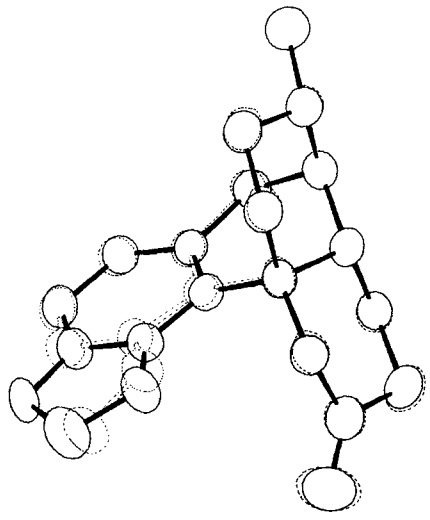


Fig. 3. *The results of the X-ray study on* **9** *are shown overlapped with the results of the X-ray study on* **28** (They show the similarities in the structure of the two molecules)

However, the X-ray results showed that both the 3,4-methylenedioxy group in **9** and the methoxy group in **28** are nearly coplanar with the aromatic rings *(Fig. 1–3)*. This is shown by the C(3)–C(4)–O(4)–C(19) torsion angle of 14.6° in **28** and the C(3)–C(4)–O(4)–C(19) and C(4)–C(3)–O(3)–C(19) torsion angles of 6.7° and −5.6°, respectively in **9**. Bonds and angles all fall within expected values for both molecules. Both molecules have the familiar T-shape exhibited by morphine and its analogs, even though the *O*-bridge is missing, and in both structures the 6-membered ring bearing the carbonyl O-atom exhibits a normal chair conformation. Packing, for both crystals, is influenced only by *Van der Waal's* forces and there are no unusually close inter-molecular approaches.

X-Ray crystallographic data of **9**. $C_{18}H_{21}NO_3$, mol. wt. = 299.37. Orthorhombic, $a = 7.062$ (4), $b = 13.722$ (8), $c = 15.269$ (9) Å, $V = 1479.7$ (8) Å^3, $Z = 4$. Space group $P2_12_12_1$, $d_{calc} = 1.34$ g cm^{-3}.

The 1149 independent intensities were measured to 2θ max = 112° with a computer-controlled diffractometer *(Nicolet P3F)* using Ni-filtered Cu$K\alpha$ radiation with a graphite monochromator on the incident beam. The structure was solved using direct methods [12]. Refinement using the restrained least-squares program CONLSQ [13] on coordinates and thermal parameters for the 22 non-H-atoms and on coordinates for the 21 H-atoms resulted in a final *R*-factor of 8.3% for all the data ($R_w = 7.7\%$).

X-Ray crystallographic data of **28**. $C_{18}H_{23}NO_2$, mol. wt. = 282.36. Orthorhombic, $a = 7.076$ (10), $b = 13.463$ (10), $c = 15.780$ (15) Å, $V = 1503.3$ (6) Å^3, $Z = 4$. Space group $P2_12_12_1$, $d_{calc} = 1.24$ g cm^{-3}.

The 1162 independent intensities were measured to a 2θ max = 112° under the same conditions as used for **9**. The structure was solved by using **9** as a partial structure and recycling with the tangent formula [14] and refined using CONLSQ in the same manner as for **9**. The final *R*-factor for **28** was 6.4% ($R_w = 7.5\%$).

Biological evaluation. – Compounds **27**, **28**, **17**, **22**, and **19** were found to be more potent than morphine *(Table)*. As noted in other series of opiates, the *N*-phenethyl substituent, as in **27**, increases antinociceptive potency considerably. The 5-methyl group in **19** appeared to cause a decrease in potency (as compared with **17**). Compounds **15**, **25**, and **26** were found to be comparable to dihydrothebainone in potency. Compounds **23** and **9** were about as potent as codeine. The

Table. *Antinociceptive Activity of the 6-Morphinanones*

Compound	ED_{50}[a])	Compound	ED_{50}[a])
8	Inactive[b])	**24**	39.7 (24.1–65.4)
9	21.1 (14.4–30.8)	**25**	6.1 (5.1–7.4)
14	80.2 (61.7–104.3)	**26**	8.9 (6.4–12.6)
15	6.0 (4.3–8.0)	**27**	0.29 (0.21–0.37)
16	66.8 (51.4–86.7)	**28**	0.90 (0.71–1.1)
17	1.1 (0.86–1.5)	Dihydrothebainone	8.0 (5.6–11.3)
19	2.0 (1.5–2.7)	Morphine	2.9 (2.5–3.3)
22	1.8 (1.3–2.4)	Codeine	17.3 (11.3–25.7)
23	16.3 (12.1–21.4)		

[a]) Antinociceptive activity determined by hot-plate assay, s.c. injection [16–18]. The ED_{50}, the effective dose at which half the mice are effected, values are in μmol/kg. The parenthesized numbers are 95% standard error limits determined by computerized probit analysis. The bases were introduced in dil. HCl solution, the salts in aq. solution.

[b]) Only 30% of the mice were effected at 350 μmol/kg.

antinociceptive potency of **22** and **23** is less than that of comparable compounds without the C(14)–OH group [1]. The remaining compounds, **24**, **16**, **14**, and **8**, all with N–H moieties, were much less potent than codeine; compound **8** was essentially inactive.

It is apparent that 6-morphinanones with a methoxy-substituted aromatic ring are potent antinociceptives. It is also apparent that, although the methoxy group, or groups, at C(4) or C(3) and C(4), respectively, aid in procuding potent antinociceptive activity, they are not absolutely required for that activity. Thus, compound **22**, without an O-atom on the aromatic ring, is about twice as potent as morphine. The 6-keto group as noted earlier [1], appears to be sufficient for potent antinociceptive action in **22**. The O-atoms on the aromatic ring do, however, aid in binding to the opiate receptors from rat brain membrane preparations. Thus, compound **19**, with a 3,4-dimethoxy-substituted aromatic ring binds with three times the affinity of **22**, and six times the affinity of **23**. Unlike the 6-keto group, the C(14)–OH does not aid in the affinity of morphinans to the opiate receptors. The ratio of the affinity of the compound to the affinity of morphine for these receptors from rat brain membrane preparations was 7.5, 24, and 47, respectively, for compounds **19**, **22**, and **23** [15]. All three compounds had less affinity for the receptors than morphine.

Experimental Part

General remarks. See [19]. Moreover: Optical rotations (concentrations (g/100 ml), solvent; average experimental error ±0.5%): *Perkin-Elmer 241 MC* polarimeter.

*(–)-4,5-Epoxy-3-hydroxy-*N*-(2,2,2-trichloroethoxycarbonyl)morphinan-6-one* (**2**). To a well-stirred suspension of 10.0 g (35 mmol) of **1** and 51.2 g (0.51 mol) of anh. $KHCO_3$ in 390 ml of $CHCl_3$, 22 g (105 mmol) of 2,2,2-trichloroethyl chloroformate was added dropwise during 20 min under Ar. The mixture was refluxed for 2 h, then stirred overnight at RT. The inorg. precipitate was filtered off and washed with $CHCl_3$. The combined org. layers were washed with 1% HCl-solution, H_2O and sat. NaCl-solution. $CHCl_3$ was evaporated *in vacuo*, and the residue was dissolved in 200 ml of MeOH and rendered alkaline (pH 8) with 20% KOH-solution. It was then stirred at RT. for 1.5 h. MeOH was evaporated under reduced pressure and the residue treated with $CHCl_3$ (200 ml). The org. layer was washed with 1% HCl-solution and H_2O, dried, and evaporated. The oily residue was treated with 60 ml of Et_2O, which caused the precipitation of a crystalline solid. The solid was filtered and digested with 50 ml of Et_2O at RT. for 5 min to give 12.05 g (77%) of **2**, m.p. 213–215°; $[\alpha]_D^{26} = -196°$ ($c = 1.25$, $CHCl_3$). – IR. (KBr): 3250 br. (OH); 1670, 1720 (CO). – ^{1}H-NMR. ($CDCl_3$): 6.78 (*d*, $J = 8$, 1 H, arom. H); 6.60 (*d*, $J = 8$, 1 H, arom. H); 6.44 (br. *s*, 1 H, HO); 4.78 (*m*, 2 H, CH_2). – MS. (CI., NH_3): 463 ($M^+ + 18$), 465 ($M^+ + 2 + 18$), 467 ($M^+ + 4 + 18$).

$C_{19}H_{18}Cl_3NO_5$	Calc.	C 51.08	H 4.06	N 3.14	Cl 23.81%
(446.73)	Found	„ 51.21	„ 4.14	„ 3.24	„ 23.49%

(–)-4,5-Epoxy-3-hydroxymorphinan-6-one (**3**). A mixture of 10 g (36.9 mmol) of **2** and 6 g (91.8 mmol) of activated Zn-powder, in 170 ml of 90% AcOH-solution, was stirred overnight at RT. The solid was filtered off and washed with glacial AcOH until the *Dragendorff* test was negative. The combined filtrates were evaporated to dryness and treated with 50 ml of 5% HCl-solution followed by 100 ml of $CHCl_3$. The layers were separated, and the aq. layer was kept in the refrigerator overnight, to give a white solid which was filtered and dried. It was recrystallized from 30 ml of hot H_2O to give 5.41 g (78.5%) of **3** · HCl, m.p. >300° ([3]: 345–350°); $[\alpha]_D^{26} = -126°$ ($c = 0.47$, H_2O) ([3]: $[\alpha]_D^{20} = -128°$ ($c = 0.537$, H_2O)). The salt was dissolved in 25 ml of hot H_2O and rendered alkaline (pH 7–8) with 30% NH_4OH-solution while hot: 4.2 g (70%) of **3** was collected, m.p. 300° ([3]: 305–306°).

*(–)-4,5-Epoxy-*N*-formyl-3-hydroxymorphinan-6-one* (**4**). A mixture of 4.2 g (15.5 mmol) of **3** in 30 ml of anh. formic acid was refluxed for 1 h under Ar, then the excess of formic acid was distilled off and the residue heated slowly (1 h) in an oil bath to 190° (bath temp.). This temp. was maintained for 1 h. The cooled solid was ground in a mortar and then washed on a funnel with *ca.* 100 ml of 5% HCl-solution and with H_2O until neutral, to give 4.13 g (90.5%) of solid, white **4**, after drying. Compound **4** was used for further transformations without purification. An analytical sample of **4** was prepared by recrystallization from glacial AcOH, m.p. >300° (dec.); $[\alpha]_D^{26} = -277°$ ($c = 1.12$, $CHCl_3$). – IR. (KBr): 3520 (OH), 1720 (ketone), 1640 (NCHO). – ^{1}H-NMR. (D_6-DMSO): 9.27 (*s*, 1 H, HO); 8.13 and 7.98 (2 *s*, 1 H, CHO, pair of rotamers); 6.60 (*d*, $J = 8$, 1 H, arom. H); 6.53 (*d*, $J = 8$, 1 H, arom. H); 4.86 (*s*, 1 H, H–C(5)). – MS. (EI.): 299 (M^+).

$C_{17}H_{17}NO_4$ (299.33) Calc. C 68.21 H 5.72 N 4.68% Found C 67.91 H 5.98 N 4.27%

*(–)-3-Benzyloxy-4,5-epoxy-*N*-formylmorphinan-6-one* (**5**). A mixture of **4** (3.8 g, 12.7 mmol) in 26 ml of anh. DMF, anh. K_2CO_3 (2.45 g, 17.7 mmol) and benzyl chloride (2.69 g, 21.2 mmol) was stirred under Ar at 90° for 7 h, then at RT. overnight. It was poured on 100 g of ice, the gum collected and dissolved in 250 ml of benzene. This solution was washed with water, 5% HCl- and sat. NaCl-solution, dried and evaporated. The resulting oil was crystallized from EtOH to give 3.72 g (75%) of **5**, m.p. 164–165°; $[\alpha]_D^{26} = -245°$ ($c = 0.93$, $CHCl_3$). – IR. (KBr): 1730 (ketone), 1650 (NCHO). – ^{1}H-NMR. ($CDCl_3$): 8.18 and 8.02 (2 *s*, 1 H, CHO, pair of rotamers); 7.38 (*m*, 5 H, 5 arom. H); 6.78 (*d*, $J = 8$, 1 H, arom. H); 6.58 (*d*, $J = 8$, 1 H, arom. H); 5.26 (*s*, 2 H, CH_2); 4.64 (*s*, 1 H, H–C(5)). – MS. (EI.): 389 (M^+).

$C_{24}H_{23}NO_4$ (389.46) Calc. C 74.02 H 5.95 N 3.60% Found C 74.09 H 5.85 N 3.88%

*(–)-*N*-Formyl-3,4-dihydroxymorphinan-6-one* (**6**). NH_4Cl (24.5 g, 0.46 mol) was added to a solution of 4.13 g (13.8 mmol) of **4** in 290 ml of EtOH, and the mixture was heated to reflux. To this heterogeneous system, activated Zn-powder (3.59 g, 53 mmol) was added portionwise within 2 h. A second portion of zinc (3.59 g, 53 mmol) was added in one batch, and the mixture was refluxed overnight. After cooling, the catalyst was filtered off and washed with EtOH. The combined filtrates were evaporated to dryness, sat. Na_2SO_4-solution (30 ml) was added, and the slurry extracted several times with a total of 400 ml of $CHCl_3$/2-propanol 3:1. The org. extracts were dried and concentrated under reduced pressure. The precipitate was filtered off, giving 3.54 g (82.5%) of **6**, which was used for further reactions without purification. An analytical sample was obtained by recrystallization from glacial AcOH, m.p. 279–282° (dec.); $[\alpha]_D^{26} = -200°$ ($c = 0.85$, DMF). – IR. (KBr): 3210 (OH), 1685 (ketone), 1640 (NCHO). – ^{1}H-NMR. (D_6-DMSO): *ca.* 9.0 (br. *s*, 1 H, HO); 7.98 (*s*, 1 H, CHO); 6.61 (*d*, $J = 7$, 1 H, arom. H); 6.39 (*d*, $J = 7$, 1 H, arom. H). – MS. (EI.): 301 (M^+).

$C_{17}H_{19}NO_4$ (301.35) Calc. C 67.76 H 6.35 N 4.65% Found C 67.68 H 6.30 N 4.65%

*(–)-*N*-Formyl-3,4-methylenedioxymorphinan-6-one* (**7**). Under Ar, 2.17 g (7.2 mmol) of **6** was dissolved in warm, anh. DMF. After cooling, 0.72 ml (11.3 mmol) of bromochloromethane was added, followed by 1.40 g (14.4 mmol) of K_2CO_3 and 145 mg (1.8 mmol) of cupric oxide. This mixture was stirred at 90° (bath temp.) for 6 h. A second batch of 0.72 ml of bromochloromethane was added through the condenser, and the mixture was stirred overnight at RT. Solvents were distilled off, and the solid residue was kept at 150° for 1 h. After cooling, the residue was partitioned between 30 ml of H_2O and 250 ml of benzene. The org. layer was washed with water, 5% HCl- and sat. NaCl-solution, dried and evaporated to give 1.68 g of a yellowish crystalline solid, that (after filtration through 16.8 g of alumina (grade II)) gave 1.37 g (60%) of pure **7**, m.p. 244–246° (subl.) from CH_2Cl_2/isopropyl ether; $[\alpha]_D^{26} = -223°$ ($c = 1.07$, $CHCl_3$). – IR. (KBr): 1710 (ketone), 1655 (NCHO). – ^{1}H-NMR. ($CDCl_3$): 8.20 and 8.05 (2 *s*, 1 H, CHO, pair of rotamers); 6.69 (*d*, 1 H, arom. H); 6.59 (*d*, $J = 8$, 1 H, arom. H); 5.93 (*s*, 2 H, OCH_2O). – MS. (EI.): 313 (M^+).

$C_{18}H_{19}NO_4$ (313.36) Calc. C 68.99 H 6.11 N 4.47% Found C 69.16 H 6.26 N 4.24%

(–)-3,4-Methylenedioxymorphinan-6-one (**8**). A solution of 810 mg (2.58 mmol) of **7** in 22 ml of MeOH and 3 ml of 37% HCl-solution was refluxed for 6 h under Ar and then evaporated. The residue was partitioned between 30% NH_4OH-solution and benzene. The org. layer was washed with water, dried and evaporated to give 570 mg (77%) of **8** as crystalline solid. An analytical sample of **8** was

obtained by digesting with hexane, m.p. 106–108°; $[\alpha]_D^{26} = -96°$ ($c = 0.85$, $CHCl_3$). – IR. (KBr): *ca.* 3050–3600 (NH). – ^{1}H-NMR. ($CDCl_3$): 6.65 (*d*, $J = 7$, 1 H, arom. H); 5.90 and 5.88 (2 *s*, 2 H, OCH_2O). – MS. (EI.): 285 (M^+).

$C_{17}H_{19}NO_3$ (285.35) · ½ H_2O Calc. C 69.37 H 6.85 N 4.76% Found C 69.09 H 6.91 N 4.96%

(–)-N-Methyl-3,4-methylenedioxymorphinan-6-one (**9**). A mixture of 400 mg (1.4 mmol) of **8**, 0.35 ml of 37% formalin, 480 mg (5.8 mmol) of NaOAc and 60 mg of 10% Pd/C in 13 ml of 2N AcOH was hydrogenated at RT. at 40 psi for 20 h. The catalyst was filtered off, washed with AcOH, and the solvents were evaporated to dryness; the residue was partitioned between benzene and 2% NaOH-solution. The org. layer was washed with water, dried, and evaporated to give 360 mg (85%) of crystalline **9**, m.p. 225–227° (subl.) after recrystallization from EtOH; $[\alpha]_D^{26} = -112°$ ($c = 1.03$, $CHCl_3$). – IR. (KBr): 1700 (ketone). – ^{1}H-NMR. ($CDCl_3$): 6.60 (*m*, 2 H, 2 arom. H); 5.90 and 5.87 (2 *s*, 2 H, OCH_2O); 2.41 (*s*, 3 H, CH_3N). – MS. (EI.): 299 (M^+).

$C_{18}H_{21}NO_3$ (299.37) Calc. C 72.22 H 7.07 N 4.68% Found C 72.52 H 6.78 N 4.45%

Compound **8** was also prepared from **6** in a one-pot procedure in 85% yield. Intermediate **7** was not isolated in this procedure, but after hydrolysis of **6** and evaporation of solvents the residue was hydrogenated in the same manner as described above.

(–)-3-Benzyloxy-N-formyl-4-hydroxymorphinan-6-one (**10**). NH_4Cl (6.85 g, 128 mmol) was added to a solution of compound **5** (1.52 g, 3.9 mmol) in 75 ml of 1-propanol, containing 4 ml of H_2O, and the mixture was heated to reflux. To this heterogenous system, activated Zn-powder (0.99 g, 15.2 mmol) was added portionwise within 2 h. A second portion of Zn (0.99 g, 15.2 mmol) was added in one batch, and the mixture was refluxed overnight (*ca.* 17 h). After cooling, the catalyst was filtered off and washed with 1-propanol. The combined filtrates were evaporated to dryness, sat. Na_2SO_4-solution was added, and this slurry was extracted with $CHCl_3$ (150 ml). The combined org. extracts were washed with water, 1% HCl- and sat. NaCl-solution. After drying and evaporation of the solvent, 1.6 g of white foam was obtained, which after dissolution in EtOH (15 ml) deposited 1.28 g (84%) of **10** as a white crystalline solid, m.p. 197–199°; $[\alpha]_D^{26} = -169°$ ($c = 0.45$, $CHCl_3$). – IR. (KBr): 3300 (OH), 1715 (ketone), 1650 (NCHO). – ^{1}H-NMR. ($CDCl_3$): 8.16 and 8.00 (2 *s*, 1 H, CHO, pair of rotamers); 7.38 (*s*, 5 H, 5 arom. H); 6.76 (*d*, $J = 8$, 1 H, arom. H); 6.54 (*d*, $J = 8$, 1 H, arom. H); 6.30 (*s*, 1 H, HO); 5.02 (*s*, 2 H, CH_2). – MS. (EI.): 391 (M^+).

$C_{24}H_{25}NO_4$ (391.47) Calc. C 73.64 H 6.44 N 3.58% Found C 73.82 H 6.46 N 3.75%

(–)-3-Benzyloxy-N-formyl-4,6-dimethoxy-5,6-didehydromorphinan (**11**). A solution of 2.18 g (5.2 mmol) of **10** in 20 ml of anh. DMF was introduced dropwise to a mixture of 312 mg (13 mmol) of NaH and 2.42 g (13 mmol) of methyl *p*-toluenesulfonate in 20 ml of anh. DMF. This mixture was stirred under Ar at RT. overnight, then poured on 75 g of ice while stirring. The white precipitate was filtered off and exhaustively washed with H_2O giving 2.13 g (91%) of pure **11**, m.p. 67–69°; $[\alpha]_D^{26} = -120°$ ($c = 0.46$, $CHCl_3$). – IR. (KBr): 1660 (NCHO). – ^{1}H-NMR. ($CDCl_3$): 8.16 and 8.00 (1 H, 2 *s*, CHO, pair of rotamers); 7.40 (*m*, 5 H, 5 arom. H); 6.80 (*m*, 2 H, 2 arom. H); 5.47 (*s*, 1 H, olef. H); 5.07 (*s*, 2 H, CH_2). – MS. (EI.): 419 (M^+).

$C_{26}H_{29}NO_4$ (419.53) · ½ H_2O Calc. C 72.87 H 7.06 N 3.27% Found C 73.14 H 7.09 N 3.07%

(–)-N-Formyl-3,4,6-trimethoxy-5,6-didehydromorphinan (**12**). A solution of 2.11 g (7 mmol) of **6** in 26 ml of anh. DMF was added dropwise to a mixture of 0.675 (28 mmol) of NaH and 5.21 g (28 mmol) of methyl *p*-toluenesulfonate in 26 ml of anh. DMF. This mixture was stirred under Ar at RT. overnight, then poured on 90 g of ice and extracted with a total of 250 ml of Et_2O. The ether extracts were washed with sat. NaCl-solution, dried and evaporated to give 2.4 g (100%) of a colorless material, that was recrystallized from Et_2O/hexane, m.p. 136–136.5°; $[\alpha]_D^{26} = -180°$ ($c = 0.89$, $CHCl_3$). – IR. (KBr): 1655 (NCHO). – ^{1}H-NMR. ($CDCl_3$): 8.0 (*s*, 1 H, CHO); 6.77 (*s*, 2 H, 2 arom. H); 5.45 (*s*, 1 H, olef. H). – MS. (EI.): 343 (M^+).

$C_{20}H_{25}NO_4$ (343.43) Calc. C 69.95 H 7.34 N 4.08% Found C 69.85 H 7.10 N 4.29%

(–)-3-Benzyloxy-4-methoxymorphinan-6-one (**13**). A solution of 210 mg (0.5 mmol) of **11** in 5 ml of MeOH containing 0.5 ml of 37% HCl-solution was refluxed for 20 h. The solution was then concentrated to 3 ml and kept at 4° overnight for crystallization. Crystalline **13** · HCl (160 mg, 77%) was obtained,

m.p. 140–142°; $[\alpha]_D^{26} = -24°$ ($c = 0.48$, MeOH). – IR. (KBr): 3520–3350 (NH_2^+), 1715 (ketone). – ^{1}H-NMR (D_6-DMSO): 9.54 (br. *s*, 2 H, NH_2^+); 7.40 (*m*, 5 H, 5 arom. H); 7.05 (*d*, $J = 7$, 1 H, arom. H); 6.90 (*d*, $J = 7$, 1 H, arom. H); 3.84 (*s*, 3 H, CH_3O). – MS. (EI.): 377 (M^+).

$C_{24}H_{27}NO_3 \cdot HCl \cdot H_2O$	Calc.	C 66.73	H 7.00	N 3.24	Cl 8.21%
(431.97)	Found	„ 67.07	„ 6.96	„ 3.35	„ 8.08%

(−)-3-Hydroxy-4-methoxymorphinan-6-one (**14**). To a solution of 1.2 g (2.86 mmol) of **11** in 15 ml of MeOH, 15 ml of 37% HCl-solution was added, and this mixture was refluxed under Ar for 5 h. MeOH was then evaporated, and the aq. solution was extracted with Et_2O (3 × 15 ml). The aq. layer was concentrated to ⅓ volume and kept in the refrigerator overnight. The white precipitated solid was filtered and washed with MeOH/Et_2O 2:3 giving 500 mg (51%) of **14** · HCl, m.p. > 300°; $[\alpha]_D^{26} = -47°$ ($c = 0.73$, MeOH). – IR. (KBr): 3500–2600 (OH, NH_2^+), 1700 (ketone). – ^{1}H-NMR. (D_2O): 6.90 (*s*, 2 H, 2 arom. H); 3.84 (*s*, 3 H, CH_3O). – MS. (EI.): 287 (M^+).

$C_{17}H_{21}NO_3 \cdot HCl$	Calc.	C 63.05	H 6.85	N 4.33	Cl 10.95%
(323.81)	Found	„ 62.84	„ 6.92	„ 4.47	„ 10.64%

A mixture of 103 mg (0.25 mmol) of **13**, 2 ml of MeOH and 2 ml of 37% HCl-solution was refluxed for 5 h under Ar. MeOH was evaporated and the residue extracted with Et_2O (2 × 3 ml). The aq. layer was concentrated to ⅓ volume *in vacuo* and left for crystallization. Pure **14** · HCl (60 mg; 74%) was collected, identical (IR., MS., m.p., TLC.) with the sample prepared from **11**.

*(−)-3-Hydroxy-4-methoxy-*N*-methylmorphinan-6-one* (**15**). A mixture of 265 mg (0.81 mmol) of **14**, 0.3 ml of aq. 37% formalin, 410 mg (5 mmol) of NaOAC, and 50 mg of 10% Pd/C in 16 ml of 2N AcOH was hydrogenated at RT. at 45 psi for 17 h. The catalyst was filtered off, washed with 2N AcOH and the filtrate evaporated to dryness. The residue was partitioned between $CHCl_3$ and H_2O, the pH adjusted to 7–8 with 30% NH_4OH-solution and the aq. layer extracted with $CHCl_3$ till *the Dragendorff* test was negative. After drying and evaporation of the solvent, 210 mg (85%) of crystalline **15** was obtained. It was recrystallized from CH_2Cl_2/hexane, m.p. 233–234° (subl.); $[\alpha]_D^{26} = -98°$ ($c = 0.62$, $CHCl_3$). – IR. (KBr): 3440 (OH), 1700 (ketone). – ^{1}H-NMR. ($CDCl_3$): 6.75 (*s*, 2 H, 2 arom. H); 4.77 (br. *s*, 1 H, HO); 3.84 (*s*, 3 H, CH_3O); 2.40 (*s*, 3 H, CH_3N). – MS. (EI.): 301 (M^+).

$C_{18}H_{23}NO_3$ (301.39) Calc. C 71.73 H 7.69 N 4.65% Found C 71.42 H 7.40 N 4.72%

Compound **15** could be prepared also from **13** in a one-pot procedure in 89% yield and without isolation of the intermediate **14**. After hydrolysis of **13** and evaporation, the residue was *N*-methylated as described above.

(−)-3,4-Dimethoxymorphinan-6-one (**16**) [10][2]. A mixture of 687 mg (2 mmol) of **12**, 20 ml of MeOH and 2 ml of 37% HCl-solution was refluxed overnight. Solvents were evaporated and the residue partitioned between 2% NaOH-solution and benzene. The aq. layer was extracted with benzene till the *Dragendorff* test was negative. The combined org. layers were washed with H_2O, dried and evaporated to give 448 mg of a foam. A solution of 420 mg (1.4 mmol) of this foam in EtOH was treated with 90 mg (0.7 mmol) of oxalic acid, dissolved in a minimum amount of EtOH. The oxalate of **16** was collected as colorless needles (330 mg; 68%), m.p. 194–197° (dec.); $[\alpha]_D^{26} = -43°$ ($c = 0.57$, MeOH). – IR. (KBr): 3400–2550 (OH, NH_2^+), 1710 (ketone). – ^{1}H-NMR. (D_6-DMSO): 6.90 (*d*, $J = 8$, 1 H, arom. H); 6.84 (*d*, $J = 8$, 1 H, arom. H); 5.77 (br. *s*, 3 H, HO, NH_2^+); 4.00 (*s*, 3 H, CH_3O), 3.75 (*s*, 3 H, CH_3O). – MS. (EI.): 301 (M^+).

$C_{18}H_{23}NO_3 \cdot \frac{1}{2}(COOH)_2 \cdot H_2O$	Calc.	C 62.62	H 7.19	N 3.84%	
(301.39)	Found	„ 62.88	„ 7.33	„ 4.01%	

*(−)-3,4-Dimethoxy-*N*-methylmorphinan-6-one* (**17**). A mixture of 182 mg (0.5 mmol) of the oxalate salt of **16**, 0.15 ml of 37% formalin, 205 mg (2.5 mmol) of NaOAc and 25 mg of 10% Pd/C in 8 ml of 2N AcOH was hydrogenated at RT. at 45 psi for 17 h. The catalyst was filtered off, washed with 2N AcOH and the filtrate evaporated to dryness. The residue was partitioned between benzene and 5% NaOH-solution, phases were separated and the aq. layer extracted with benzene till the *Dragendorff* test was negative. After drying and evaporation of the solvent, 130 mg (82%) of crystalline **17** were

[2]) No physical data were reported in [10].

obtained, m.p. 117–118° after recrystallization from Et_2O ([12]: m.p. 116.5–117.5°); $[\alpha]_D^{26} = -90°$ ($c = 0.63$, $CHCl_3$). – IR. (KBr): 1710 (ketone). – ^{1}H-NMR. ($CDCl_3$): 6.73 (*m*, 2 H, 2 arom. H); 3.90 (*s*, CH_3O); 3.77 (*s*, 3 H, CH_3O); 2.36 (*s*, 3 H, CH_3N). – MS. (EI.): 315 (M^+).

$C_{19}H_{25}NO_3$ (315.42) Calc. C 72.35 H 7.99 N 4.44% Found C 72.45 H 7.63 N 4.51%

Compound **17** was prepared also from **12** in a one-pot reaction in 87% yield. In this procedure the intermediate **16** was not crystallized after hydrolysis, but after evaporation of solvents directly *N*-methylated in the manner described above.

*(–)-N-Cyclopropylmethyl-3,4-dimethoxymorphinan-6-one hydrobromide (**26** · HBr).* To a mixture of 900 mg (2.35 mmol) of **16** · HBr, and 1.8 g (13.0 mmol) of anh. K_2CO_3 in 15 ml of anh. DMF 0.24 ml (2.60 mmol) of cyclopropylmethyl chloride were added. This mixture was stirred under Ar for 5.5 h at 100° (bath temp.), filtered and washed with $CHCl_3$. The filtrate was evaporated, partitioned between H_2O and Et_2O, the org. layer dried and evaporated to yield **26** as an oil. The hydrobromide salt of **26** (740 mg; 72%) was formed in the usual way. An analytical sample was recrystallized from acetone, m.p. 262–266° (dec.); $[\alpha]_D^{25} = -64°$ ($c = 1.03$, EtOH). – IR. (KBr): 1708 (ketone). – ^{1}H-NMR. (D_6-DMSO): 6.94 (*d*, $J = 8$, 1 H, arom. H); 6.82 (*d*, $J = 8$, 1 H, arom. H); 3.86 (*s*, 3 H, CH_3O); 3.82 (*s*, 3 H, CH_3O). – MS. (CI.): 356 ($M^+ + 1$).

$C_{22}H_{29}NO_3 \cdot HBr$ Calc. C 60.55 H 6.93 N 3.21 Br 18.31%
Found „ 60.58 „ 7.19 „ 3.25 „ 18.14%

*(–)-3,4-Dimethoxy-N-phenethylmorphinan-6-one hydrobromide (**27** · HBr).* A mixture of 1.0 g (2.61 mmol) of **16** · HBr, 2 g (14.4 mmol) of anh. K_2CO_3, and 0.39 ml (2.85 mmol) of phenethyl bromide in 20 ml of anh. DMF was stirred at 100° (bath temp.) for 16 h. After filtration, the filtrate was evaporated and the residue partitioned between H_2O and CH_2Cl_2. The org. layer was dried and evaporated to give 860 mg of an oil, which was converted to 880 mg (69%) of **27** · HBr in the usual way. An analytical sample was prepared by recrystallization from MeOH, m.p. 253–256° (dec.); $[\alpha]_D^{25} = -64°$ ($c = 0.81$, EtOH). – IR. (KBr): 1715 (ketone). – ^{1}H-NMR. (D_6-DMSO): 9.90 (br. *s*, 1 H, NH^+); 7.25 (*s*, 5 H, 5 arom. H); 6.90 (*m*, 2 H, 2 arom. H); 3.86 (*s*, 3 H, CH_3O); 3.82 (*s*, 3 H, CH_3O). – MS. (CI.): 406 ($M^+ + 1$).

$C_{26}H_{31}NO_3 \cdot HBr$ Calc. C 64.19 H 6.63 N 2.88 Br 16.43%
(486.44) Found „ 63.94 „ 6.75 „ 2.84 „ 16.79%

*(–)-3,4-Dimethoxy-N-5-dimethylmorphinan-6-one hydrobromide (**19** · HBr).* A mixture of 1.4 g (4.4 mmol) of **18**, 355 mg of 60% dispersion of NaH (6.8 mmol) in oil, and 1.52 g (8.8 mmol) of phenyltrimethylammonium chloride in 15 ml of anh. DMF was stirred under Ar at 80° (bath temp.) for 3 h. After cooling, the mixture was filtered, washed with $CHCl_3$ and MeOH, and the filtrate was evaporated. The residue was dissolved in 1N HCl, washed with Et_2O (discarded), rendered alkaline with 30% NH_4OH-solution and extracted with CH_2Cl_2. The org. layer was dried and evaporated to give 1.44 g of **19** as an oil. The hydrobromide salt of **19** (1.33 g, 73%) was formed in the usual way. An analytical sample was recrystallized from MeOH/Et_2O, m.p. 251–253° (dec.); $[\alpha]_D^{25} = -19°$ ($c = 1.00$, H_2O). – IR. (KBr): 1700 (ketone). – ^{1}H-NMR. (D_6-DMSO): 6.96 (*d*, $J = 8$, 1 H, arom. H); 6.84 (*d*, $J = 8$, 1 H, arom. H); 4.08 (*qa*, $J = 7$, 1 H, H–C(5)); 3.85 (*s*, 3 H, CH_3O); 3.36 (*s*, 3 H, CH_3O); 3.98 (*s*, 3 H, CH_3N); 1.24 (*d*, $J = 7$, 3 H, H_3C–C(5)). – MS. (EI.): 329 (M^+).

$C_{20}H_{27}NO_3 \cdot HBr$ Calc. C 58.54 H 6.88 N 3.41 Br 19.47%
(410.35) Found „ 58.43 „ 7.06 „ 3.70 „ 19.36%

*(–)-14-Hydroxy-N-methyl-4-[(1-phenyl-1H-tetrazol-5-yl)oxy]morphinan-6-one (**21**).* A mixture of 5 g (18.4 mmol) of **20**, 5 g (36.2 mmol) of anh. K_2CO_3 and 3.35 g (18.6 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole in 50 ml of anh. DMF was stirred at RT. under Ar for 17 h. The mixture was filtered, washed with $CHCl_3$ and the filtrate evaporated. The residue was dissolved in CH_2Cl_2, washed with 1N NaOH and sat. NaCl-solution, dried and evaporated to give an oil, which crystallized from EtOAc to yield 5.25 g (70%) of **21**, m.p. 185–187°; $[\alpha]_D^{24} = -33°$ ($c = 0.98$, $CHCl_3$). – IR. (KBr): 3400 (OH), 1714 (ketone). – ^{1}H-NMR. ($CDCl_3$): 8.04 (*m*, 2 H, 2 arom. H); 7.54 (*m*, 3 H, 3 arom. H); 7.12 (*m*, 3 H, 3 arom. H); 2.36 (*s*, 3 H, CH_3N). – MS. (EI.): 431 (M^+).

$C_{24}H_{25}N_5O_3$ (431.48) Calc. C 66.80 H 5.84 N 16.23% Found C 66.57 H 6.04 N 16.41%

*(–)-14-Hydroxy-*N*-methylmorphinan-6-one* (**22**). Pd/C (10%, 8.6 g) was added to a solution of 4.3 g (10.0 mmol) of **21** in glacial AcOH, and the mixture was hydrogenated at 50 psi at RT. for 16 h. The catalyst was filtered off, washed with AcOH, and the filtrate was evaporated. The residue was dissolved in H_2O, rendered alkaline with conc. NaOH-solution and extracted with CH_2Cl_2. The org. layer was washed with sat. NaCl-solution, dried and evaporated to give an oil, which was crystallized with EtOH to yield 2.45 g (91%) of **22**. An analytical sample was recrystallized from MeOH, m.p. 145–146°; $[\alpha]_D^{26} = -141°$ ($c = 0.80$, $CHCl_3$). – IR. (KBr): 3420 (OH), 1712 (ketone). – ^{1}H-NMR. ($CDCl_3$): 7.14 (*m*, 4 H, 4 arom. H); 2.38 (*s*, 3 H, CH_3N). – MS. (EI.): 271 (M^+).

$C_{17}H_{21}NO_2$ (271.35) Calc. C 75.24 H 7.80 N 5.61% Found C 75.28 H 7.63 N 5.20%

*(–)-*N*-Methylmorphinan-14-ol* (**23**). A mixture of 1.7 g (6.3 mmol) of **22**, 17 ml of ethylene glycol and 8.5 ml of 64% hydrazine hydrate was stirred at 125° (bath temp.) for 1.5 h. After cooling, 2.3 g of KOH pellets were added, and this mixture was stirred at 205° (bath temp.) for 2 h. After cooling, the mixture was acidified with 2N HCl, washed with Et_2O (discarded), rendered alkaline with conc. NaOH-solution and extracted with CH_2Cl_2. The org. layer was washed with sat. NaCl-solution, dried and evaporated to yield 1.55 g of a crystalline solid, which was recrystallized with MeOH to afford 1.3 g (81%) of **23**, m.p. 120°; $[\alpha]_D^{25} = -72°$ ($c = 0.95$, $CHCl_3$). – IR. (KBr): 3400 (OH). – ^{1}H-NMR. ($CDCl_3$): 7.12 (*m*, 4 H, 4 arom. H); 4.44 (br. *s*, 1 H, HO); 2.30 (*s*, 3 H, CH_3N). – MS. (EI.): 257 (M^+).

$C_{17}H_{23}NO$ (257.36) Calc. C 79.33 H 9.01 N 5.44% Found C 79.46 H 8.99 N 5.26%

*(–)-*N*-Allyl-4-hydroxymorphinan-6-one* (**25**). A mixture of 1.0 g (3.89 mmol) of **24**, 1.0 g (7.2 mmol) of anh. K_2CO_3 and 15 ml of anh. DMF followed by 0.343 ml (3.96 mmol) of allyl bromide, was stirred at 90° (bath temp.) under Ar for 30 min, and filtered. The filtrate was evaporated and the residue partitioned between $CHCl_3$ and H_2O. The org. layer was washed with H_2O and sat. NaCl-solution, dried and evaporated to give an oily residue, which was crystallized with EtOH to give 860 mg (70%) of **25**, m.p. 95–98°; $[\alpha]_D^{26} = -176.5°$ ($c = 0.97$, $CHCl_3$). – IR. (KBr): 3540 (OH), 1695 (ketone). – ^{1}H-NMR. ($CDCl_3$): 6.88 (*d* × *d*, $J = 8$, and 8, 1 H, arom. H); 6.64 (*d*, $J = 8$, 1 H, arom. H); 6.58 (*d*, $J = 8$, 1 H, arom. H); 5.84 (*m*, 1 H, $CHCH{=}CH_2$); 5.16 (*m*, 2 H, $CHCH{=}CH_2$); 4.38 (*d*, $J = 14$, 1 H, H_β–C(5)). – MS. (EI.): 297 (M^+).

$C_{19}H_{23}NO_2 \cdot H_2O$ (315.38) Calc. C 72.34 H 7.99 N 4.44% Found C 72.22 H 8.16 N 4.33%

REFERENCES

[1] *H. Schmidhammer, A. E. Jacobson & A. Brossi,* Medicinal Research Reviews, ed. G. deStevens, in press.
[2] *J. Hellerbach, O. Schnider, H. Besendorf & B. Pellmont,* in 'Synthetic Analgesics. Part II (A) Morphinans', Pergamon Press, N.Y. 1966.
[3] *I.R. Bartels-Keith & D. W. Hills,* J. Chem. Soc. C *1967,* 434.
[4] *M.D. Rozwadowska, F.-L. Hsu, A.E. Jacobson, K.C. Rice & A. Brossi,* Can. J. Chem. *58,* 1855 (1980)
[5] *M. Rösner, F.-L. Hsu and A. Brossi,* J. Org. Chem. *46,* 3686 (1981).
[6] *T.H. Gulland & R. Robinson;* J. Chem. Soc. *123,* 1009 (1923); *R.S. Cahn,* J. Chem. Soc. *1926,* 2562.
[7] *L. Small, H.M. Fitch & W.E. Smith,* J. Am. Chem. Soc. *58,* 1457 (1936).
[8] *H. Schmidhammer, A.E. Jacobson, L. Atwell & A. Brossi,* Helv. Chim. Acta *64,* 2540 (1981).
[9] *H. Schmidhammer, A.E. Jacobson & A. Brossi,* Heterocycles *17,* 391 (1982).
[10] *R.L. Clark, A.A. Pessolano, J. Weiglard & K. Pfister,* J. Am. Chem. Soc. *75,* 4963 (1953).
[11] *H. Schmidhammer, A.E. Jacobson, L. Atwell & A. Brossi,* Heterocycles *16,* 1859 (1981).
[12] *J. Karle & I.L. Karle,* Acta Crystallogr. *21,* 849 (1966).
[13] *J.L. Flippen-Anderson, J.H. Konnert & R. Gilardi,* Acta Crystallogr., in press (1982).
[14] *J. Karle,* Acta Crystallogr. B*24,* 182 (1968),
[15] *J.H. Woods, J.L. Katz, F. Medzihradsky, C.B. Smith & G.D. Winger,* 'Problems of Drug Dependence 1982', Louis S. Harris, Editor, National Institute on Drug Abuse Research Monograph Series, Washington, D.C., 1982, in press.
[16] *N.B. Eddy & D. Leimbach,* J. Pharmacol. Exp. Ther. *107,* 385 (1953).
[17] *A.E. Jacobson & E.L. May,* J. Med. Chem. *8,* 563 (1965).
[18] *L. Atwell & A.E. Jacobson,* Lab. Animal *7,* 42 (1978).
[19] *F.-L. Hsu, K.C. Rice & A. Brossi,* Helv. Chim. Acta *65,* 1576 (1982).