157. Structure Determination of Brominated Morphinan-6-ones by ^{13}C-NMR.Spectroscopy: A Novel Closure of the Oxygen Bridge Using 4-Acetoxymorphinan-6-ones

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Dedicated to Professor *George H. Büchi* on the occasion of his 60th birthday

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Summary

Bromination of (–)-4-hydroxy-*N*-methylmorphinan-6-one (**3**), prepared from natural morphine, with 1 mol of bromine in acetic acid, afforded the 1-bromo ketone **5**. The structure of **5** was assigned by ^{13}C-NMR.spectroscopy, and confirmed by X-ray diffraction analysis of its hydrobromide salt. It is suggested that monobromination of synthetic (±)-2,4-dihydroxy-*N*-formylmorphinan-6-one (**7**) takes in principle a similar course, although the ^{13}C-NMR.spectrum of the primary reaction product **9** could not be measured because of insolubility in commonly used solvents. Monobromination of (–)-4-acetoxy-*N*-formylmorphinan-6-one (**12**) of the natural series, and of (±)-2,4-diacetoxy-*N*-formylmorphinan-6-one (**8**) of the synthetic series, followed by treatment of the monobrominated ketones with potassium carbonate in methanol resulted in closure of the O-bridge, and afforded after acid hydrolysis, the corresponding 4,5-epoxy-morphinan-6-ones (–)-**16** and (±)-**17** respectively. This variation of the ring closure reaction represents a novel and convenient method to convert 4-hydroxymorphinan-6-ones into their corresponding 4,5-epoxymorphinan-6-ones, without involving aromatic bromination and with only 1 mol of bromine.

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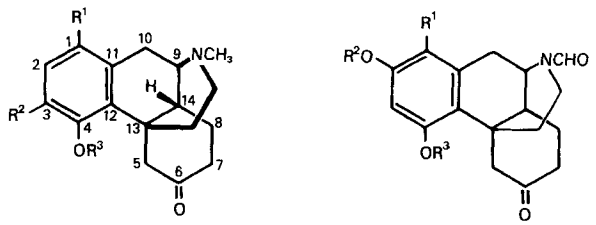
The closure of the 4,5-O-bridge in the synthesis of 3-deoxy-7,8-dihydromorphines and derivatives [1–3], utilized the bromination-dehydrobromination path already explored by several investigators in connection with the synthesis of opium alkaloids from dihydrothebainone [4]. Bromination in the dihydrothebainone series is known to occur first at the aromatic C(1), before C(7), α to the carbonyl group, undergoes substitution by bromine [4h]. Monobromination has now been demonstrated to take a similar course in the 4-hydroxymorphinan-6-one series by analysis of the ^{13}C-NMR.spectra of brominated intermediates in the present work, model substances and the 4-acetyl opioids **1** and **2** prepared from natural materials *(Tables 1–3)*. This reaction of **3** thus affords **5** as the product, the structure of which was confirmed by a single crystal X-ray analysis of the hydrobromide salt. Analysis of the ^{13}C-NMR.spectra of morphinan-6-ones **1–6** permitted assignment of all the aromatic C-atoms in these compounds *(Table 3)*. The corresponding spectra of the racemic *N*-formyl compounds **7–10** *(Scheme 1)* prepared by total synthesis were either not obtainable due to insolubility (**7** and **9**) or definitive analyses could not be obtained (**8** and **10**) due to the presence of rotamers [5–7]. It seems likely however, that bromination in the 2,4-dihydroxymorphinan-6-one series proceeds analogous to the 4-hydroxymorphinan-6-one series, *via* an initial electrophilic substitution at C(1) by bromine.

Scheme 1



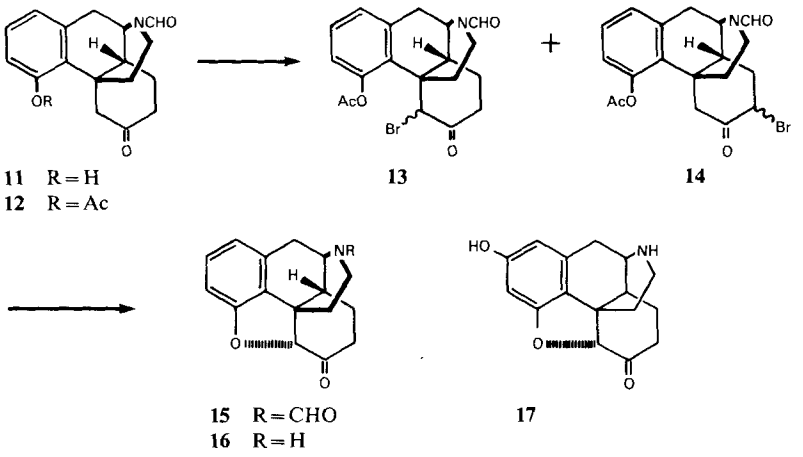
1 $R^1 = H, R^2 = OCH_3, R^3 = Ac$
2 $R^1 = Br, R^2 = OCH_3, R^3 = Ac$
3 $R^1 = R^2 = R^3 = H$
4 $R^1 = R^2 = H, R^3 = Ac$
5 $R^1 = Br, R^2 = R^3 = H$
6 $R^1 = Br, R^2 = H, R^3 = Ac$

7 $R^1 = R^2 = R^3 = H$
8 $R^1 = H, R^2 = R^3 = Ac$
9 $R^1 = Br, R^2 = R^3 = H$
10 $R^1 = Br, R^2 = R^3 = Ac$

Although C(1) bromination in the 4-hydroxymorphinan-6-one series is the initial reaction leading to O-bridge closure as reported here and by other investigators, we have now shown that O-bridge closure in this series can be accomplished *without* aromatic bromination when 4-acetoxymorphinan-6-ones are utilized as described below. When *N*-formyl monoacetate **12**, prepared from **11** of the natural series [2], was brominated with 1 mol of bromine under the usual conditions for O-bridge closure [4h] a crystalline mixture of monobromoketones was obtained. The ^{1}H-NMR.spectrum of this mixture of isomers was complex due to rotamers of each, but was suggestive of a mixture of **13** and **14**. Crystallization of this mixture from ethanol then afforded a pure monobromoketone that showed spectral characteristics consistent, but not definitive for a mixture of rotamers of a 7-bromoketone **14**. Al-

though this material proved to be chemically uniform, a crystal suitable for X-ray analysis could not be obtained, which is not surprising due to the existence of rotamers in this *N*-formyl series. Nevertheless the mixture of monobromoketones was quite suitable for further transformation and closure of the O-bridge could readily be accomplished by treatment of the mixture with potassium carbonate in methanol at room temperature.

Scheme 2



11 R = H
12 R = Ac
13
14
15 R = CHO
16 R = H
17

A sample of the *N*-formyl derivative **15** thus obtained proved to be, after two crystallizations from ethyl acetate, identical with a reference sample [2]. Acid hydrolysis of crude **15** with hydrochloric acid in methanol afforded, after usual workup, the norketone **16**, identical with a reference sample in every respect [2]. The overall yield of **16** from **11** was 44%.

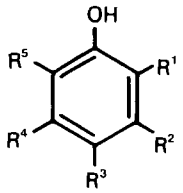
Similar treatment of the diacetate **8**, prepared from **7** of the synthetic series, afforded ketone **17**, a racemic isomer of nordihydromorphinone *(Scheme 2)*. The bromination of 4-acetoxy-*N*-formylmorphinan-6-one reported here, does not give aromatic bromination, and the formation of the O-bridge can thus be accomplished with only 1 mol of bromine and under extremely mild reaction conditions.

^{13}C-NMR.Analysis[4]*).* Initial attempts to confirm the position of the bromine in morphinan-one **5** involved the study of a number of bromophenols (**18–23**, *Scheme 3*) that were readily available and would serve as model compounds. The data for these bromophenols as well as their acetates are listed in *Tables 1* and *2*. A comparison of these data with that in *Table 3* for the morphinanones **3–6** suggested, that the bromine was located at C(1) but this location was not considered to be definitive. Confirmation of the location of the bromine at C(1) in **5** and **6**, as well as in **2**, was determined by conducting proton-coupled and long-range selective proton-decoup-

[4]) The ^{13}C-NMR.spectra were recorded on a *JEOL-FX60 FT* NMR.spectrometer (15.03 MHz) with TMS as internal standard, a 45° pulse and 5s repition rate. The LSPD.experiments were conducted by centering the decoupler at δ_H 3.0 and using a low decoupling power (~0.1W). The proton-coupled spectra were recorded using gated-decoupling (decoupler off during data acquisition).

ling experiments with the $CDCl_3$-soluble acetates **2** and **6**. The proton-coupled spectrum of **6** showed the signal for the brominated aromatic carbon (121.5 ppm) as a complex multiplet and the aromatic methine carbons as sharp doublets (123.8 ppm, $^1J_{(C,H)} = 1.660$ Hz; 131.2 ppm, $^1J_{(C,H)} = 168.9$ Hz).

Scheme 3



18 $R^1 = R^2 = R^4 = R^5 = H, R^3 = Br$
19 $R^1 = R^3 = R^4 = R^5 = H, R^2 = Br$
20 $R^1 = Br, R^2 = R^3 = R^4 = R^5 = H$
21 $R^1 = R^5 = CH_3, R^2 = R^4 = H, R^3 = Br$
22 $R^1 = R^5 = H, R^2 = R^4 = CH_3, R^3 = Br$
23 $R^1 = Br, R^2 = R^4 = R^5 = H, R^3 = CH_3$

This data is consistent with location of the bromine at C(1) in **6** and thus eliminates the other possibility at C(3). The long-range couplings of the 121.5 ppm signal were assumed to be due to the protons H–C(2), H–C(3), H–C(9) or H–C(10). If the bromine was at C(3), then the signal for C(3) would not be expected to long-range couple to the aliphatic protons H–C(9) or H–C(10) while the signal for C(1) should show evidence of this long-range coupling. A long-range selective proton decoupling (LSPD) experiment [8] with the decoupler centered near δ_H 3.0 (near the center of all the aliphatic protons) showed the signal at 121.5 ppm as double doublet. In this experiment all of the long-range aliphatic couplings are eliminated and only the long-range couplings to the aromatic protons are observed (two bond coupling to H–C(2) and three bond coupling to H–C(9). The aromatic methines appear as doublets just like in the proton-coupled spectrum. Thus, the proton-coupled and LSPD.data confirm that the bromine in the acetate **6** is at C(1) and therefore bromination of **3** results in introduction of bromine in the *para*-position to the hydroxy group.

Examination of the proton-coupled and LSPD.(irrad. at δ_H 3.0) data for **2** led to the conclusion that the bromine is located at C(1) and not at C(2). The bromine-substituted C-signal (121.2 ppm) appeared as a multiplet and the aromatic methine (115.5 ppm) appeared as a sharp doublet ($^1J_{(C,H)} = 167.5$ Hz) in the proton-doublet (two bond coupling to H–C(2) while the 115.5 ppm signal was unchanged. The proton-coupled and LSPD.experiments also allowed assignments of the signals for C(11) and C(12) in **2**. The signal at 129.2 ppm appeared as a broadened triplet ($^3J_{(C,H)} = 6.5$ Hz) while the 132.7 ppm signal appeared as a complex multiplet in the proton-coupled spectrum. The LSPD.spectrum (irrad. at $\delta_H = 3.0$) showed the 129.2 ppm signal as a doublet (three bond coupling to H–C(2) and 132.7 ppm signal as a singlet. Thus, the signal at 129.2 ppm can be assigned to C(11) and the 132.7 ppm signal to C(12).

X-Ray analysis of bromomorphinanone **5** (see *Figure*). X-ray diffraction analysis confirmed the position of the bromine atom in **5**, which was used as the hydrobromide salt. The conformation of the 1-bromo-4-hydroxymorphinan-6-one (**5**) cation with the bond lengths as determined by X-ray diffraction analysis and the X-ray numbering scheme is shown as an ORTEP-drawing [9] in the *Figure*. The molecule has the familiar T-shape exhibited by morphine and morphine analogues, even though the O-bridge is missing. Bond lengths and angles are close to those reported for comparable parts of morphine and expecially close to those found in (+)-3-methoxy-*N*-methylmorphinan [10], the C,N-skeleton of which is enantiomorphic with that of naturally occuring morphine and derivatives.

In the crystal, the molecular packing is dominated by H-bonds between the bromide anion and H–N(15) and H–O(4) of two different cations **5**, with N(15)...Br(2) = 3.153 Å and O(4)...Br(2) = 3.206 Å. The Br ion and cation **5** alternate along the *z* direction of the lattice.

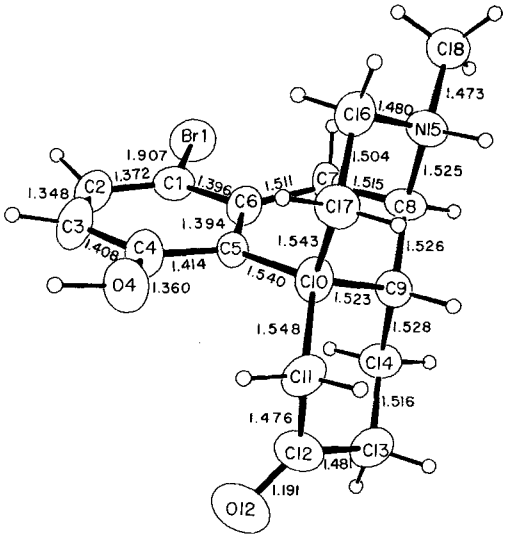


Figure. *The X-ray diffraction structure of* **5** *showing the atomic numbering, bond lengths and thermal ellipsoids at a 50% probability level* (H–Atoms are represented by arbitrary spheres. Esd's of bond lengths are less than 0.009 Å).

X-ray crystallographic data of **5**. $C_{17}H_{20}O_2NBr \cdot HBr$, mol. wt. = 350.27 + 80.93. Orthorhombic, $a = 11.346\,(2)$ A $b = 15.391\,(3)$ Å, $c = 9.685\,(2)$ Å, $V = 1691.3$ Å^3, $z = 4$. Space group $P2_12_12_1$, $d = 1.693$ g cm^{-3}.

Intensities were measured to $2\Theta_{max} = 100°$ with a computer-controlled diffractometer (*Nicolet* P3) using Ni filtered Cu K_d radiation. Including all *Friedel* pairs there were 2064 data. The structure was solved using the heavy-atom technique. Full matrix least-squares refinement on the coordinates and anisotropic thermal parameters for the 22 non-hydrogen atoms and coordinates only for the 21 H-atoms resulted in a final *R*-factor of 4.4% for all the data. Anomalous dispersion factors were included for the Br atoms.

Table 1. *^{13}C-NMR.Spectral data of bromophenol model compounds* (Scheme 3)

Compounds[a])	**18**	**19**	**20**	**21**	**22**	**23**	[c])
C-atom assignments[b])							
1	156.3 (154.2)	158.7 (156.1)	153.9 (152.4)	152.8 (151.4)	156.2 (154.1)	151.8 (150.2)	135.9 (136.1)
2	117.5 (117.3)	118.6 (119.4)	109.8 (110.3)	126.6 (125.3)	115.7 (115.4)	109.5 (109.9)	138.3 (138.5)
3	132.0 (132.6)	122.2 (123.0)	132.9 (132.1)	131.3 (131.1)	138.3 (139.6)	133.0 (132.2)	125.7 (125.7)
4	110.8 (113.2)	121.9 (124.4)	120.7 (121.8)	111.8 (112.2)	115.7 (118.4)	129.8 (131.4)	130.4 (130.3)
5	132.0 (132.6)	130.8 (130.8)	128.5 (129.2)	131.3 (131.1)	138.3 (139.6)	129.1 (129.8)	126.8[1] (126.8)
6	117.5 (117.3)	114.6 (114.4)	116.7 (116.3)	126.6 (125.3)	115.7 (115.4)	116.5 (116.0)	128.9[1] (128.9)
CH_3	–	–	–	16.0 (15.6)	23.8 (23.8)	19.8 (20.1)	19.2 (19.3) 20.9 (21.1)

[a]) All bromophenols listed were purchased from *Aldrich Chemical Co.*, Milwaukee, WI.
[b]) Assignments are based on chemical shift theory and single-frequency off-resonance decoupling. The values listed are for DMSO-d_6; those in parentheses are for $CDCl_3$.
[c]) 3-Bromo-1,2-dimethylbenzene.

Table 2. *^{13}C-NMR.Spectral data of bromo acetates*

Compounds[a])	Phenolic acetyl derivatives of					
	18	**19**	**20**	**21**	**22**	**23**
C-atom assignments[b])						
1	150.0	151.5	148.5	147.6	149.4	146.2
2	123.4	125.1	116.3	132.5	121.2	115.8
3	132.3	122.3	133.4	131.3	139.4	133.6
4	118.6	128.9[1]	128.5[1]	118.7	124.0	137.4
5	132.3	130.4[1]	127.3[1]	131.3	139.4	129.0
6	123.4	120.5	123.8	132.5	121.2	123.3
CH_3	–	–	–	16.0	23.8	20.3[1]
CH_3COO	20.7	20.8	20.6	20.2	20.2	20.5[1]
CH_3COO	168.5	158.5	168.2	168.1	168.8	168.3

[a]) The acetates were prepared from the corresponding phenols by standard acetic anhydride/pyridine treatment (OH replaced by OAc in *Scheme 3*).
[b]) Assignments are based on chemical shift theory and single-frequence off-resonance decoupling. Signals bearing the same numerical superscript may be reversed. All values were obtained in $CDCl_3$.

Table 3. *^{13}C-NMR. Spectral date for the aromatic C-atoms of morphinanones*

Compounds	**1**	**2**	**3**	**4**	**5**[b])	**6**
C-atom assignment[a])						
1	125.6	121.2	119.3	125.7	(112.9)	121.5
2	111.2	115.5	127.1 (126.3)	126.8	(130.2)	131.2
3	150.1	150.5	114.5 (113.7)	122.2	(115.8)	123.8
4	139.6	139.2	156.8 (156.4)	149.7	(155.9)	148.9
11	130.2[1]	129.2	139.0 (139.2)	139.6	(137.5)	138.5
12	130.7[1]	132.7	123.5 (123.5)	129.0	(126.2)	131.7

[a]) Assignments are based on chemical shift theory, single-frequence off-resonance decoupling, proton-couplings, and selective proton-decouplings. Signals bearing the same numerical superscript may be interchanged. The values listed are for $CDCl_3$; those in parentheses are for DMSO-d_6.

[b]) Compound **5** was practically insoluble in $CDCl_3$.

Table A. *Fractional coordinates and B_{eq} values for 1-bromo-4-hydroxymorphinan-6-one* (**5**·HBr)

Atom	x	y	z	B_{eq}
Br–C(1)	0.5323	0.4996	0.4649	4.1
Br–C(2)	0.1980	0.1495	0.0153	3.9
C(1)	0.4730	0.3879	0.4158	3.1
C(2)	0.4526	0.3719	0.2785	3.5
C(3)	0.4097	0.2936	0.2421	3.7
C(4)	0.3865	0.2279	0.3397	3.3
C(5)	0.4155	0.2423	0.4799	2.3
C(6)	0.4486	0.3262	0.5176	2.6
C(7)	0.4595	0.3524	0.6674	2.9
C(8)	0.4212	0.2847	0.7717	2.6
C(9)	0.4556	0.1937	0.7238	2.5
C(10)	0.3918	0.1720	0.5897	2.4
C(11)	0.4302	0.0791	0.5483	3.1
C(12)	0.5591	0.0671	0.5408	3.5
C(13)	0.6237	0.0947	0.6662	3.8
C(14)	0.5894	0.1856	0.7110	3.2
N(15)	0.2885	0.2863	0.7973	3.1
C(16)	0.2193	0.2600	0.6747	3.4
C(17)	0.2589	0.1726	0.6231	3.1
C(18)	0.2477	0.3690	0.8571	4.3
O(4)	0.3333	0.1516	0.3059	4.0
O(12)	0.6082	0.0359	0.4441	5.5

Table B. *Fractional coordinates for hydrogen atoms in 1-bromo-4-hydroxymorphinan-6-one* (**5**·HBr)

Atom	x	y	z
H–C(2)	0.446	0.428	0.224
H–C(3)	0.367	0.285	0.149
H_a–C(7)	0.411	0.404	0.687
H_b–C(7)	0.545	0.365	0.689
H–C(8)	0.463	0.297	0.864
H–C(9)	0.427	0.143	0.801
H_a–C(11)	0.394	0.065	0.458
H_b–C(11)	0.397	0.038	0.621
H_a–C(13)	0.713	0.098	0.649
H_b–C(13)	0.610	0.056	0.747
H_a–C(14)	0.629	0.199	0.801
H_b–C(14)	0.619	0.227	0.639
H–N(15)	0.267	0.246	0.873
H_a–C(16)	0.230	0.306	0.598
H_b–C(16)	0.132	0.259	0.696
H_a–C(17)	0.243	0.129	0.696
H_b–C(17)	0.215	0.158	0.536
H_a–C(18)	0.321	0.399	0.913
H_b–C(18)	0.182	0.359	0.925
H_c–C(18)	0.221	0.410	0.789
HO–C(4)	0.317	0.151	0.204

The esd's for x, y and z are near 0.0006, 0.0004 and 0.0007, resprectively, except for the Br atoms where they are less than 0.0001.

Experimental Part

General remarks. Physical constants and spectra were determined using the instrumentation indicated. Melting points (m.p.): *Thomas-Hoover* or *Fisher-Johns* apparatus (corrected). IR. Spectra (γ[cm^{-1}]): *Beckman* IR 4230 spectrometers. Optical rotations (concentration (g/100 ml), solvent): *Perkin-Elmer* Model 241 MC polarimeter. ^{1}H-NMR. Spectra ([ppm] relative to internal TMS, Multiplicity: *s*=singlet, *d*=doublet, *d*×*d*=doublet of doublets, *m*=multiplet, *J*[Hz]=apparent coupling constant): *Varian* HR 220 or *JOEL LNM-FX 100* spectrometer. Mass spectra (MS.) *(m/e): Finnigan* 1015D spectrometer with a Model 6000 data collection system for chemical ionization (CI.) mass spectra or *Hitachi Perkin-Elmer RMU-6E* spectrometer (70 eV) for electron ionization (EI.) mass spectra. Thin layer chromatography (TLC.): silica gel GF, *Analtech, Inc.* Column chromatography: alumina *woelm* N, Act. III, *Woelm Pharma.*

(–)-4-O-Acetyldihydrothebainone (**1**). A mixture of dihydrothebainone [4i] (1.20 g, 4.0 mmol) and acetic anhydride (10 ml) was heated at 95–100° for 2.5 h underAr, evaporated, dissolved in 10 ml of EtOAc and rendered acidic with HCl gas to afford1.40 g of crude **1**·HCl as a blue-gray solid. A solution of this material in 15 ml of H_2O was stirred 5 min with 0.5 g of *Norite,* filtered through *Celite* and the filter washed with 10 ml of H_2O. The stirred pale yellow filtrate was treated at 0° with 25 ml of $CHCl_3$ and a minimum amount of conc. aq NH_3-solution to adjust the pH of the aq. phase to 9–9.5. The $CHCl_3$ was separated and the aq. phase saturated with NaCl and extracted with 3 times 20 ml of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and evaporated to a yellow foam that was heated to solution in 15 ml of dry $N(C_2H_5)_3$ and seeded (with material initially obtained crystalline from ether in an earlier run) to give pure **1** (534 mg, 39%), m.p. 96.5–97.5°; $[\alpha]_D^{23}$–51.5° (*c*=1.9, $CHCl_3$). – IR ($CHCl_3$): 1762 (ester), 171$_2$ (ketone), 1480. – ^{1}H-NMR. (220 MHz, $CDCl_3$): 2.35 (*s*, 3H, CH_3COO or NCH_3); 2.41 (*s*, 3H, CH_3COO or NCH_3); 3.67 (*d*, *J*=13, 1H, H$_\beta$–C(5)); 3,72 (*s*, 3 H, CH_3O); 6.55 (*d*, *J*=8.5, 1H, arom. H), 6.96 (*d*, *J*=8.5, 1 H, arom H). – MS. (EI.): 343 (*M*$^+$), 300 (*M*$^+$–CH_3CO).

Treatment of **1** in EtOAc with a slight excess of HCl gas in EtOH afford **1**·HCl, m.p. 265–266.5° (dec.) (lit [11] m.p. 244–245°).

$C_{20}H_{25}NO_4$ (343.41) Calc. C 69.95 H 7.34 N 4.08% Found C 70.11 H 7.21 N 4.07%

(–)-4-Acetyl-1-bromodihydrothebainone (**2**). Treatment of 1-bromodihydrothebainone [4a] (760 mg, 2.0 mmol) with 10 ml of acetic anhydride was carried out as described above for **1**. Evaporation and decolorization with 350 mg of *Norite* in 10 ml of H_2O and work-up as for **1** gave crude **2** which was crystallized from Et_2O to give pure **2** (580 mg, 69%), m.p. 155.5–157.5° $[\alpha]_D^{23}$=–59.1° (*c*=2.1, $CHCl_3$). –IR. ($CHCl_3$): 1762 (ester), 1714 (ketone), 1462. – ^{1}H-NMR. (220 MHz, $CDCl_3$): 2.34 (*s*, 3H, CH_3COO or NCH_3); 2.41 (*s*, 3H, CH_3 COO or NCH_3);3.67 (*d*, *J*=13, 1H, Hβ–C(5)); 3.75 (*s*, 3H, CH_3O); 7.31 (*s*, 1H, arom. H). – MS. (EI.): 421/423 (*M*$^+$), 378/380 (*M*$^+$–CH_3CO).

$C_{20}H_{24}BrNO_4$ (422.31) Calc. C 56.88 H 5.73 N 3.32% Found C 56.54 H 5.37 N 3.47%

*(–)-4-Acetoxy-*N*-methylmorphinan-6-one* (**4**). A mixture of **3** [2] (800 mg, 2.95 mmol), acetic anhydride (8 ml) and pyridine (15 ml) was stirred at RT. overnight. Acetic anhydride and pyridine were evaporated i.V. and the resulting crude product was taken into toluene and evaportated. This residue was then partitioned between $CHCl_3$ and H_2O. The organic extracts were dried (Na_2SO_4) and evaporated to give a gum which was crystallized from diisopropyl ether/hexane to afford **4** (482 mg, 65%). An analytical pure material was recrystallized from diisopropyl ether, m.p. 96–97°. – IR. (KBr): 1763 (ester), 1710 (ketone). – ^{1}H-NMR. (220 MHz, $CDCl_3$): 2.36 (*s*, 3H, CH_3COO or NCH_3); 2.42 (*s*, 3H, CH_3COO or NCH_3); 3.64 (*d*, *J*=14, 1H, Hβ–C(5)), 6.84 (*d*, *J*=7, 1H, arom. H), 6.99 (*d*, *J*=7, 1H, arom. H), 7.11 (*d*×*d*, *J*=7, 7, 1H, arom. H). – MS. (EI.): 313 (*M*$^+$), 270 (*M*$^+$–CH_3CO).

$C_{19}H_{23}NO_3$ (313.40) Calc. C 72.82 H 7.40 N 4.47% Found C 72.64 H 7.60 N 4.24%

*(–)-1-Bromo-4-hydroxy-*N*-methylmorphinan-6-one* (**5**). To a solution of **3** [2] (1.0 g, 3.7 mmol) in 30 ml of AcOH was added a solution of Br_2 in acetic acid (0.1M, 37 ml, 3.7 mmol) dropwise at RT. The mixture was stirred for 15 min and acetic acid was evaporated i.V. The residue was treated with toluene and evaporated to give a solid which was recrystallized from H_2O to afford **5**·HBr·½H_2O (625 mg, 50%), m.p. 218–221°, $[\alpha]_D^{20}$=–52.9° (*c*=1.00, CH_3OH). – IR (KBr): 3300 (OH), 1700 (C=O). – ^{1}H-NMR. (100 MHz, CD_3OD): 2.97 (*s*, 3H, NCH_3); 4.30 (*d*, *J*=14, 1H, H$_\beta$–C(5)); 6.63 (*d*, *J*=9.5, 1H, arom. H), 7.31 (*d*, *J*=9.5, 1H, arom. H). – MS. (CI.): 349/351 (*M*$^+$)

$C_{17}H_{20}BrNO_2 \cdot HBr \cdot ½H_2O$ (440.18)	Calc.	C 46.39	H 5.04	N 3.18	Br 36.31%
	Found	„ 46.25	„ 5.33	„ 2.91	„ 36.43%

Free base **5**, m.p. 222–224° (CH_3OH), $[\alpha]_D^{20} = -66.1°$ ($c = 1.14$, DMSO). – IR. (KBr): 3200 (OH), 1710 (C=O). – ^{1}H-NMR.(100 MHz, DMSO-d_6): 2.28 (*s*, 3H, NCH_3); 4.08 (*d*, $J = 14$, 1H, H_β–C(5)); 6.56 (*d*, $J = 9$, 1H, arom. H), 7.21 (*d*, $J = 9$, 1H, arom. H). – MS. (EI.): 349/351 (M^+).

$C_{17}H_{20}BrNO_2$	Calc.	C 58.30	H 5.76	N 4.00	Br 22.81%
(350.26)	Found	„ 58.58	„ 5.76	„ 4.14	„ 22.61%

*(–)-4-Acetoxy-1-bromo-*N*-methylmorphinan-6-one* (**6**). Compound **6** was obtained, in the same way as described for **4**, from **5** (500 mg, 1.16 mmol), acetic anhydride (5 ml) and pyridine (10 ml). The crude product was recrystallized from diisopropyl ether to yield **6** (262 mg, 58%), m.p. 159–161°, $[\alpha]_D^{20} = -57.6°$ ($c = 0.78$, $CHCl_3$). – IR. (KBr): 1755 (ester), 1715 (ketone). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 2.37 (*s*, 3H, CH_3COO or NCH_3); 2.42 (*s*, 3H, CH_3COO or NCH_3); 3.64 (*d*, $J = 14$, 1H, H_β–C(5)); 6.78 (*d*, $J = 9.5$, 1H, arom. H); 7.42 (*d*, $J = 9.5$, 1 H, arom. H). – MS. (EI.): 391/393 (M^+), 348/350 (M^+–CH_3CO).

$C_{19}H_{22}BrNO_3$ (392.29) Calc. C 58.17 H 5.65 N 3.57% Found C 57.88 H 5.90 N 3.74%

*(±)-2,4-Diacetoxy-*N*-formylmorphinan-6-one* (**8**). A mixture of **7** [3] (2.4 g, 8 mmol), acetic anhydride (65 ml) and pyridine (130 ml) was stirred at RT. overnight. The work-up was identical to that for **4**. The crude product was recrystallized from benzene/petroleum ether to yield **8** (2.5 g, 81.5%), m.p. 178–180°. – IR. (KBr): 1780,1765 (ester), 1710 (ketone) 1665 (amide). – ^{1}H-NMR. (220 MHz, $CDCl_3$): 2.26 and 2.39 (2*s*, 3H each, 2 CH_3COO); 3.64 (*d*, $J = 13$, 1H, H_β–C(5)); 6.82 (*s*, 2H, arom.H); 8.04 and 8.20 (2*s*, 1H, NCHO). – MS. (EI.): 385 (M^+).

$C_{21}H_{23}NO_6$ (385.42) Calc. C 65.44 H 6.02 N 3.63% Found C 65.20 H 5.79 N 3.69%

*(±)-1-Bromo-2,4-dihydroxy-*N*-formylmorphinan-6-one* (**9**). Compound **7** (1 g, 3.32 mmol) was dissolved in 300 ml of hot AcOH. The solution was cooled to RT. and treated with a solution of Br_2 in AcOH (0.1M, 33.2 ml, 3.32 mmol) dropwise. After the addition was completed the mixture was stirred for 15 min and a white precipitate was formed. This heterogeneous mixture was stirred for another 30 min and AcOH was then evaporated to give a pale yellow solid which was recrystallized from CH_3OH/H_2O to afford **9** (1.07 g, 85%), m.p. 260–262° (dec.). – IR. (KBr): 3200 (OH), 1690 (ketone), 1645 (amide). – ^{1}H-NMR. (100 MHz, DMSO-d_6 + CD_3OD): 6.39 (*s*, 1H, arom. H), 7.92 and 8.09 (2*s*, 1H, NCHO).– MS. (EI.): 379/381 (M^+).

$C_{17}H_{18}BrNO_4$	Calc.	C 53.70	H 4.77	N 3.68	Br 21.01%
(380.25)	Found	„ 53.55	„ 5.04	„ 3.33	„ 21.40%

*(±)-1-Bromo-2,4-diacetoxy-*N*-formylmorphinan-6-one* (**10**). Treatment of **9** (400 mg, 1.05 mmol) with acetic anhydride (8 ml) and pyridine (16 ml) following a procedure similar to that for the preparation of **4** gave the crude product which was recrystallized from CH_3OH/diisopropyl ether to yield **10** (298 mg, 61%), m.p. 186–187°. – IR. (KBr): 1765, 1750 (ester), 1700 (ketone), 1660 (amide). – ^{1}H-NMR. (220 MHz, $CDCl_3$): 2.32 and 2.38 (2*s*, 3H each, 2 CH_3COO); 3.66 (*d*, $J = 13$, 1H, H_β–C(5)); 6.90 and 6.93 (2*s*, 1H, arom. H), 8.03 and 8.19 (2*s*, 1H, NCHO). – MS. (EI.): 463/465 (M^+).

$C_{21}H_{22}BrNO_6$	Calc.	C 54.32	H 4.78	N 3.02	Br 17.21%
(464.32)	Found	„ 54.36	„ 4.92	„ 3.18	„ 17.57%

*(–)-4-acetoxy-*N*-formylmorphinan-6-one* (**12**). Compound **11** [2] (2.12 g, 7.4 mmol) was converted to **12** by a similar procedure for the preparation of **4**. This workup gave an oil which was crystallized from EtOH to afford pure **12** (1.85 g, 76%), m.p. 153–155°, $[\alpha]_D^{26} = -146.8°$ ($c = 1.11$, $CHCl_3$). – IR. (KBr): 1770 (ester), 1710 (ketone), 1655 (amide). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 2.36 (*s*, 3H, CH_3COO); 3.66 (*d*, $J = 13$, 1H, H_β–C(5)), 6.86–7.25 (3H, arom. H), 8.00 (*s*, 1H, NCHO). – MS. (EI.): 327 (M^+).

$C_{19}H_{21}NO_4$ (327.37) Calc. C 69.70 H 6.47 N 4.28% Found C 69.54 H 6.48 N 4.15%

*Bromination of (–)-4-acetoxy-*N*-formylmorphinan-6-one* (**12**). To a solution of **12** (327 mg, 1 mmol) in 4 ml AcOH was added a solution of Br_2 in AcOH (0.1M, 10 ml, 1.0 mmol) dropwise at RT. during 15 min. The solution was evaporated i.V. and the oily residue was partitioned between $CHCl_3$ and 2N NaOH. The organic layer was separated, washed with sat. NaCl-solution, dried and evaporated to give a foam (400 mg). Upon treatment with EtOAc, 200 mg of a 1:1 mixture of **13** and **14** could be crystallized, m.p. 158–162°. – IR. (KBr): 1765 (ester), 1715 (ketone), 1665 (amide). – ^{1}H-NMR. (100 MHz, $CDCl_3$): 2.38 (*s*, 3H, CH_3COO); 4.20 (*m* 0.5H); 5.72 (*s*, 0.5H); 6.85–7.25 (*m* 3H, arom. H); 8.00 (*s*, 1H, NCHO). – MS. (EI.): 405/407 (M^+).

$C_{19}H_{20}BrNO_4$ (406.27) Calc. C 56.17 H 4.96 N 3.45% Found C 55.99 H 4.89 N 3.35%

Once a recrystallization of above mixture from EtOH gave a pure material (**13** or **14**), m.p. 183–184°. – ^{1}H-NMR. (100 MHz, $CDCl_3$): 2.38 (*s*, 3H, CH_3COO); 3.58 (*d*, J=13, 1H); 4.20 (*m*, 1H); 6.85–7.25 (*m*, 3H, arom. ArH); 8.03 and 8.20 (2*s*, 1H,NCHO).

(–)-4,5-Epoxymorphinan-6-one (**16**) from **12**. The crude product (foam, 400 mg) of the bromination of **12** (327 mg,1 mmol) was dissolved in 20 ml MeOH and treated with K_2CO_3 (500 mg). The mixture was stirred at RT. for 1 h and the solvent was then evaporated to give a residue which was taken into 10 ml H_2O and extracted with $CHCl_3$. The combined organic layers were washed with sat. NaCl-solution, dried, and evaporated to give the crude product **15** as a foam (230 mg) which in a separate experiment was crystallized from EtOAc to give pure **15** that was identical with a reference sample [2]. Without purification, crude **15** was refluxed with 18 ml MeOH and 2 ml 37% HCl-solution for 6 h. MeOH was evaporated and the residue rendered alkaline with conc. NaOH-solution and extracted with $CHCl_3$. The combined organic layers were washed with sat. NaCl-solution, dried, and evaporated to give a solid which was recrystallized from ether to afford **16** (150 mg, 59%), m.p. 160–161°, which was identical with the authentic sample [2].

(±)-4,5-Epoxy-2-hydroxymorphinan-6-one (**17**). To a solution of **8** (772 mg, 2.0 mmol) in 20 ml AcOHwas added a solution of Br_2 in AcOH (0.1M, 20 ml, 2.0 mmol) dropwise at RT. The mixture was stirred for 15 min and AcOH was evaporated i.V. to afford a gum. This brominated crude product was washed with ether and the residue was evaporated to give a pale yellow foam [MS. (EI.): 463/465] which was dissolved in 30 ml MeOH and treated with anhydrous K_2CO_3 (1.6 g, 11.6 mmol) and stirred under N_2 at RT. for 15 min. MeOH was evaporated and the residue was taken into 10 ml 5% NaOH-solution and washed with ether. This basic solution was rendered acidic with conc. HCl-solution and extracted with $CHCl_3$/isopropyl alcohol 3 :2. The organic layer was washed with sat. NaCl-solution, dried, and evaporated to afford a light brown solid (250 mg) as a complicated mixture. Acid hydrolysis of this *N*-formyl intermediate for 4 h with a mixture of 2 ml of 37% HCl-solution and 20 ml MeOH, evaporation, addition aq. NH_3-solution to pH 9 and extraction with $CHCl_3$/isopropyl alcohol 3 :2 gave a light brown solid which was purified by preparative TLC. (silica gel, $CHCl_3$/MeOH/conc. NH_4OH-solution 30 :20 :1) to afford **17** (90 mg, 17%), m.p. >200° (gradually darkens). –IR. (KBr): 3400 (OH), 3280 (NH), 1720 (C=O).– ^{1}H-NMR. (100 MHz, DMSO-d_6) 4.68 (*s*, 1H, H_β-(5));6.04 (*s*, 2H, arom. H). – MS. (CI.): 271(M^+).

$C_{16}H_{17}NO_3 \cdot \frac{1}{2}H_2O$	Calc.	C 68.63	H 6.30	N 4.60%
(280.33)	Found	„ 68.35	„ 6.36	„ 5.00%

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