DIRECT α-BROMINATION OF MORPHINAN-6-ONE BASES

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Abstract —— Bromination of morphinan-6-one base in the presence of HBr afforded α-bromoketone without aromatic substitution. This method may be applicable to other basic compounds, such as alkaloids, except for compounds having acid-sensitive functional groups.

Morphine and morphinan chemistry continue to offer attractive themes of study for pharmacological activities. In bromination in the morphinan-6-one series under the usual condition, aromatic substitution occurs before α-bromination of the carbonyl group. Brossi et al.[1] reported the preparation of α-bromoketone without aromatic bromination using N-formyl compound as a starting material. This report prompted us to describe our results concerning direct α-bromination of morphinan-6-one bases. Since α-bromination of a ketone is usually performed under the acid-catalyzed condition, we tried bromination of morphinan-6-one in the presence of a catalytic amount of HBr. Pyridinium hydrobromide perbromide (PPB)[2] was used as a brominating reagent, partly because the procedure is simple and safe and partly because the stoichiometric treatment is reproducible even in a small-scale experiment.
This method may be applicable to other alkaloids to obtain α-bromoketone without aromatic substitution.

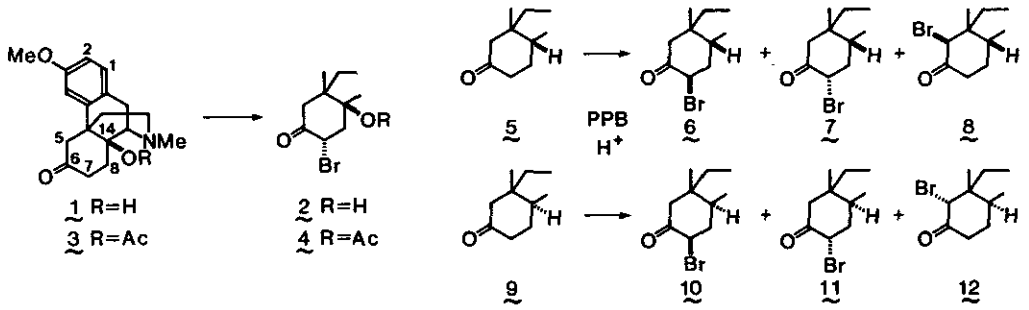
TYPICAL PROCEDURE

To a stirred solution of (-)-14-hydroxy-3-methoxy-6-oxo-N-methylmorphinan (1)[3] (301 mg, 1 mmole) in acetic acid (5 ml) in the presence of 48% HBr (0.12 ml, 1.05 equiv.), PPB (320 mg, 1 mmole) was added as one portion. After stirring

† Deceased.

for 15 min at room temperature, ether was added to the colorless solution to precipitate the oily product, which was dissolved in water and neutralized with aqueous ammonia. Extraction with dichloromethane gave crude 7α-bromoketone 2 (366 mg, 96%), mp 198°C (decomp.) which on recrystallization from ethanol afforded the pure product (275 mg, 72%), mp 214°C (decomp.).

Five morphinan ketones were tested. Since three aromatic protons appeared as ABX or ABC pattern in the ^{1}H-NMR spectra of the monobromoketones, no aromatic substitution occurred under this acid-catalyzed condition. The position and configuration of the bromine atom introduced were determined by the signal shape and J-value(s) (Table 1), as well as by the carbonyl band in the IR spectrum and by the CD value.



1 R=H
3 R=Ac

2 R=H
4 R=Ac

5 6 7 8 9 10 11 12

Table 1

Substrate	Bromoketone	IR (cm^{-1})	CD[θ] (nm)	^{1}H-NMR (δ) (J, Hz)
1	7α (eq) 2	1731	-13800 (282)	5.14 (7β-H, 12.5, 7.0)
3	7α (eq) 4	1730	-18300 (288)	4.74 (7β-H, 13.5, 6.5)
5	7β (ax) 6*	--	--	4.18 (7α-H, td, 3.5, 1.0),
	7α (eq) 7*	--	--	4.74 (7β-H, dd, 12.5, 7.0),
	5β (ax) 8*	--	--	4.97 (5α-H, d, 1.0)
9	7α (ax) 10*	--	--	4.43 (7β-H, m, $W_{1/2}$ 8.0),
	7β (eq) 11*	--	--	4.75 (7α-H, dd, 13.5, 7.0),
	5α (ax) 12*	--	--	4.50 (5β-H, m, $W_{1/2}$ 3.0)
13	8β (eq) 14	1730	+2240 (285)	4.44 (8α-H, d, 13.0)

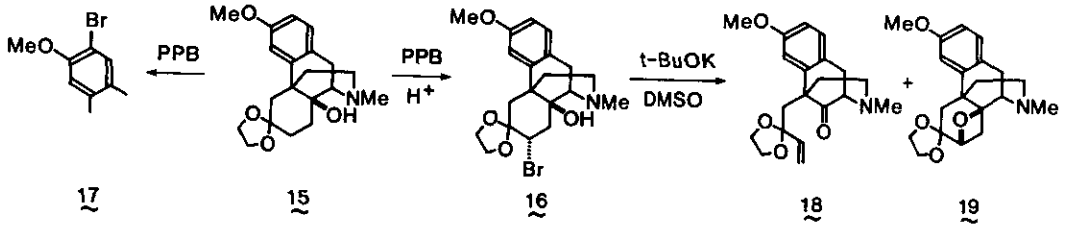
* Unseparable mixture. Detected by ^{1}H-NMR spectrum.

BROMINATION OF (-)-14β-HYDROXY-6-KETAL (15)

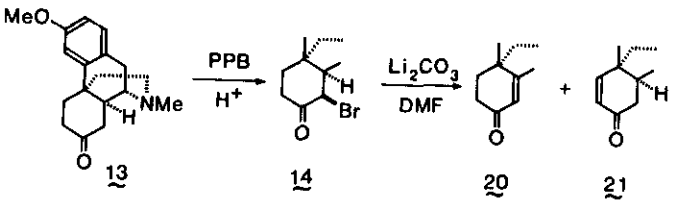
a) With HBr. The ethylenedioxy compound is often used as a starting material

for the α-bromoketone. Under the same conditions described above, 15 afforded the bromoketal 16, which after treatment with an acid (partial hydrolysis of the ketal function occurred during the reaction), gave a bromoketone which was identified as 2, obtained from 1.

b) Without HBr. With 3 equiv. of PPB, the ketal 15 afforded a monobromo ketal, which after acid treatment gave 2-bromoketone 17: IR (ν, $CHCl_3$) 1715 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, ppm) 7.29 and 6.77 (s, 1-H and 4-H). With 1 equiv. of PPB, the reaction was not complete, showing two spots [(15) and (17)] on TLC.



17 15 16 18 19



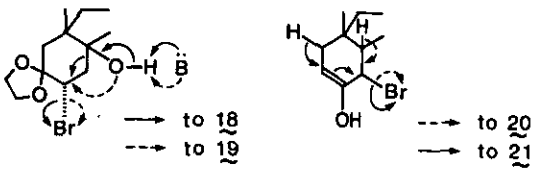
13 14 20 21

DEHYDROBROMINATION OF BROMOKETONES

a) (-)-14β-Hydroxy-7α-bromo-6-one (2). General procedures using lithium salt or collidine for dehydrobromination of the bromoketone 2 were not successful, giving the starting material or intractable mixtures.

b) (-)-14β-Hydroxy-7α-bromo-6-ketal (15). When the t-BuOK-DMSO system was used as a base, the bromoketal 15 gave two separable products. The oily one proved to be a vinyl ketoketal 18 based on its spectral data: IR (ν, $CHCl_3$)

[Fig. 1]



1734 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$) 5.88, 5.21, and 5.03 ppm (ABX, vinyl group). The other product was determined to be an epoxyketal 19 by mechanistic consideration (Fig. 1) and the disappearance of the hydroxyl band in the IR spectrum.

c) (-)-14βH-8β-Bromo 7-one (14). According to the general procedure for dehydrobromination, 14 afforded two conjugated ketones, Δ^8-7-one 20 and Δ^5-7-one 21, the structures of which were determined by IR and ^{1}H-NMR spectra: 20, IR (1676 cm^{-1}), ^{1}H-NMR [5.98 ppm (s, 8-H)]; 21, IR (1678 cm^{-1}), ^{1}H-NMR [7.26 and 6.03 ppm (5-H and 6-H, ABq, J = 10.0 Hz)] (Fig. 1).

EXPERIMENTAL

(-)-7α-Bromo-14-hydroxy-3-methoxy-6-oxo-N-methylmorphinan (2). mp 214°C (decomp.); $[\alpha]_D$ -40.7°; Anal. found C, 57.25, H, 5.97, N, 3.74, Br, 21.37%, calcd. for $C_{18}H_{22}NO_3Br$ C, 56.85, H, 5.83, N, 3.68, Br, 21.01%.

(-)-14-Acetoxy-7α-bromo-3-methoxy-6-oxo-N-methylmorphinan (4). mp 202°C (decomp.); $[\alpha]_D$ -97.9°; Anal. found C, 57.12, H, 5.87, N, 3.45, Br, 18.81%, calcd. for $C_{20}H_{24}NO_4Br$ C, 56.88, H, 5.73, N, 3.32, Br, 18.92%.

(+)-8β-Bromo-3-methoxy-7-oxo-N-methylmorphinan (14). mp 111-113°C; Anal. found C, 59.32, H, 6.07, N, 3.82, Br, 22.18%, calcd. for $C_{18}H_{22}NO_2Br$ C, 59.34, H, 6.09, N, 3.85, Br, 21.94%.

Bromination of (-)-6-ethylenedioxy-14-hydroxy-3-methoxy-N-methylmorphinan (15).

a) PPB (1 equiv.) with HBr --- After bromination of the ketal 15 (345 mg) described above, the reaction product was hydrolyzed with dil. HCl. Recrystallization of the crude product (291 mg), mp 195°C (decomp.) gave a bromoketone mp 214°C (decomp.) which proved to be bromoketone 2.

b) PPB (3 equiv.) without HBr --- To a solution of the ketal 15 (345 mg) in AcOH (5 ml) was added PPB (960 mg). After stirring for 4 h at room temperature, the reaction mixture was treated in the usual way and hydrolyzed with dil. HCl. Recrystallization of the crude product gave 2-bromoketone 17 (295 mg, 79%): mp 190-191°C; $[\alpha]_D$ -87.9°; IR 1715 cm^{-1}; ^{1}H-NMR (δ, $CDCl_3$, ppm) 7.29 and 6.77 (s, 1-H and 4-H); Anal. found C, 57.00, H, 5.89, N, 3.95, Br, 21.38%, calcd. for $C_{18}H_{22}NO_3Br$ C, 56.85, H, 5.83, N, 3.68, Br, 21.01%.

Dehydrobromination of (-)-7α-bromo-6-ethylenedioxy-14-hydroxy-3-methoxy-N-methylmorphinan (16). A solution of the bromoketal 16 (424 mg) and t-BuOK (220 mg) in DMSO (5 ml) was stirred at room temperature for 9 h. The reaction mixture was poured into water (60 ml) and subjected to extraction with benzene. The crude

product (374 mg) was then separated by preparative TLC.

Product A: 5-(3-ethylenedioxy-1-butenyl)-2'-methoxy-2-methyl-9-oxo-6,7-benzomorphan (18), oil, 121 mg (35%).

Product B: 7,14-epoxy-6-ethylenedioxy-3-methoxy-N-methylmorphinane (19), 138 mg (40%); mp 167-169°C; $[\alpha]_D$ -38.5°; ^{1}H-NMR (δ, $CDCl_3$) 4.16 ppm (br-d, J = 6.5 Hz, 7-H); Anal. found C, 70.05, H, 7.57, N, 3.94%, calcd. for $C_{20}H_{25}NO_4$ C, 69.95, H, 7.33, N, 4.08%. When a solution of the epoxyketal 19 (200 mg) in 10% HBr (2 ml) was refluxed for 30 min, the product obtained in almost quantitative yield was proved to be bromoketone 2 (228 mg), mp 216°C (decomp.) by the IR spectrum, mp and mixed mp.

Dehydrobromination of (+)-8β-bromo-3-methoxy-7-oxo-N-methylmorphinan (14). A solution of the bromoketone 14 (1.8 g) and lithium carbonate (1.1 g) in DMF (20 ml) was refluxed for 2 h. The reaction mixture was then poured into water (300 ml) and subjected to extraction with benzene. The crude product (1.4 g) was separated on a preparative TLC plate:

(+)-3-Methoxy-7-oxo-Δ^8-N-methylmorphinan (20): amorphous; 540 mg (39%); IR 1676 and 1640 cm^{-1}; ^{1}H-NMR 5.98 ppm (s, 8-H).

(+)-3-Methoxy-7-oxo-Δ^5-N-methylmorphinan (21): mp 117-118°C; IR 1678 cm^{-1}; ^{1}H-NMR 7.26 and 6.03 ppm (ABq, J = 10.0 Hz, 5-H and 6-H).

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