AN EFFICIENT SYNTHESIS OF 14-HALOGENOMETHYL-SUBSTITUTED C-NORMORPHINANS

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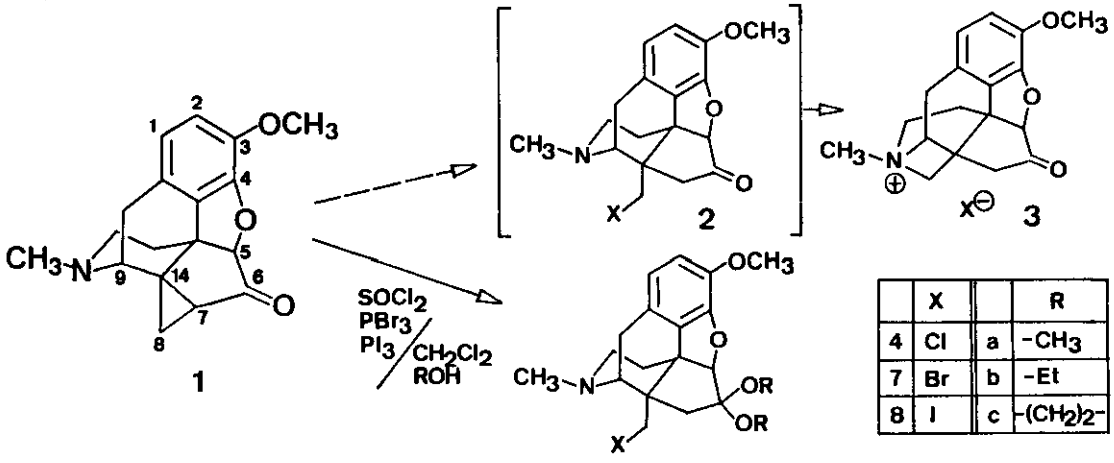
Abstract - Nucleophilic ring-opening reaction of 7,14-cyclo-dihydrocodeinone 1 resulted in a water-soluble quaternary ammonium salt 3. However, similar reaction of 1 under acetalization conditions led to the ring cleavaged 14-halogenomethylacetals 4, 7 and 8 (a-c) in high yields. When the acetals were hydrolyzed, the formation of cyclic ammonium compounds (3) was unavoidable.

Following our interest in the chemistry of C-normorphinans, we investigated the reactivity of the cyclopropane moiety in 7,14-cyclo-dihydrocodeinone[1] 1 towards nucleophiles.



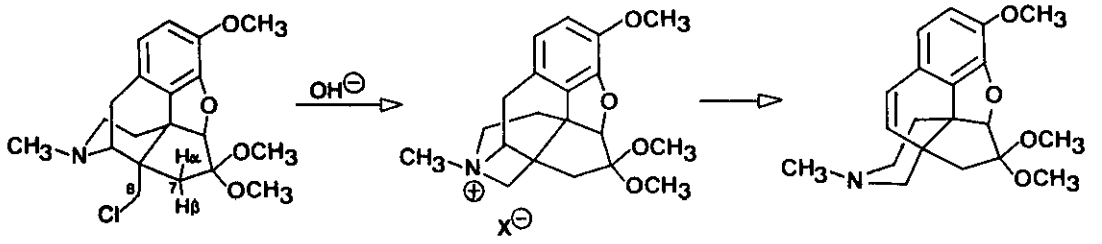
	X		R
4	Cl	a	-CH_3
7	Br	b	-Et
8	I	c	-$(CH_2)_2$-

Under the conditions of "electrophile-assisted nucleophilic ring-opening"[2-4], complete reaction occurred but no product was available from the organic layer after workup. There was every reason to believe that the ring-opening product 2 was readily transformed to the water-soluble quaternary ammonium salt 3. In addition, the nmr-analysis of the aqueous layer confirmed this presumption.

It was unexpected that a ring-opening product could be obtained in excellent yields when thionyl chloride as reagent and dichloromethane and methanol as solvents were used. The nmr-spectrum of this compound 4a showed a dd-signal of one proton at 4.95 ppm (H-8a) which was in correlation with an electron-withdrawing substituent at C-8. The geminal proton H-8b gave a doublet at 3.78 ppm. The second coupling of H-8a was caused by a long-range coupling with H-7α which was additionally splitted by geminal coupling with H-7β. Furthermore, the doublet of the H-7β at 2.16 ppm and the two singlets of the acetal-methyls were detectable. The structure 4a was further affirmed by the ^{13}C-nmr and the mass spectrum.

Intramolecular alkylation of the nitrogen occurred only when 4a was reacted with alcoholic alkali solutions. It was possible to isolate 5 as perchlorate (5a) but the Hofmann-degradation proceeded quickly to give 6 under these conditions.

Acidic hydrolysis of the product 4a afforded a water-soluble quaternary ammonium salt (3) via intramolecular cyclization.



4a

5 : $X^{\ominus} = Cl^{\ominus}, OH^{\ominus}$
5a: $X^{\ominus} = ClO_4^{\ominus}$

6

When phosphorus tribromide was used as nucleophile under the described conditions (dichloromethane and methanol as solvents) the 14-bromomethyl-acetal was also available (7a). The iodo-compound (8a) could be obtained by use of phosphorus triiodide as reagent. Furthermore, the ethyl- and ethylene-acetals (4b, 4c, 7b, 7c, and 8b) could be prepared with ethanol or ethylene glycol as alcohol component.

The observation that the formation of the acetals prevents the intramolecular alkylation of the nitrogen is subject of further investigations.

EXPERIMENTAL

All melting points were determined on a KOFLER melting point apparatus and are uncorrected. Infrared spectra were measured on a PERKIN-ELMER 298 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded on BRUKER AC 80 and WP 250, using deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a VARIAN MAT CH-7 by Dr. Nikiforov, Institut für Organische Chemie. Microanalyses were performed by Dr. Zak, Institut für Physikalische Chemie.

(5R,9R,13R,14S)-14-Chloromethyl-4,5-epoxy-3-methoxy-17-methyl-C-normorphinan-6-one Dimethylacetal (4a)

A solution of 7,14-cyclodihydrocodeinone (1.0 g, 3.4 mM) in 30 ml of dry dichloromethane (distilled over P_2O_5) and 5 ml of abs. methanol was cooled to -20 °C. Fresh distilled thionyl chloride (3 ml, 41 mM) was added slowly unter a steam of N_2. The cooling bath was removed and the stirring was continued for 2 h. The mixture was then poured into a solution of sodium hydroxide (7.0 g) in 200 ml of water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and evaporated. Crystallization from methanol gave 4a (1.25 g, 98 %) as

colorless crystals: mp 113 °C; ^{1}H-nmr [$CDCl_3$] δ 6.76, 6.63 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 4.95 (dd, 1H, J = 3 Hz, J = 10 Hz, 8a-H), 4.52 (s, 1H, 5-H), 3.93 (s, 3H, arom. OCH_3); 3.78 (d, 1H, J = 10 Hz, 8b-H), 3.31 (s, 6H, acetal-OCH_3), 2.39 (s, 3H, N-CH_3), 2.16 (d, 1H, J = 14 Hz, 7β-H), 0.96 (dd, 1H, J = 3 Hz, J = 14 Hz, 7α-H); ^{13}C-nmr [$CDCl_3$] δ 146.1 (4-C), 142.9 (3-C), 131.7 (12-C), 127.5 (11-C), 118.9 (1-C), 114.8 (2-C), 110.2 (6-C), 94.1 (5-C), 57.6 (18-C), 56.9 (9-C), 52.2 (14-C), 50.7, 49.4 (acetal-C), 48.6 (8-C), 45.8, 45.7 (13-C and 16-C), 43.6 (17-C), 38.0 (7-C), 27.7, 20.8 (10-C and 15-C); ms (m/z) 379/381 (M^+). Anal. Calcd for $C_{20}H_{26}O_4NCl$: C, 63.23; H, 6.89; N, 3.68. Found: C, 63.06; H, 6.84; N, 3.45.

(5R,9R,13R,14S)-14-Chloromethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Diethylacetal (4b)

Synthesis of **4b** was carried out as described for **4a** with addition of 5 ml of abs. ethanol instead of methanol. Colorless crystals from ethanol (1.23 g, 90 %): mp 157 °C; ^{1}H-nmr [$CDCl_3$] δ 6.79, 6.66 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 5.00 (dd, 1H, J = 3 Hz, J = 10 Hz, 8a-H), 4.54 (s, 1H, 5-H), 3.93 (s, 3H, arom. OCH_3), 3.86 - 3.23 (q,q, 2H, 2H, acetal-CH_2-), 2.39 (s, 3H, N-CH_3), 1.23, 1,06 (t,t, 3H, 3H, J = 7.5 Hz, acetal-CH_3); ms (m/z) 407/409 (M^+). Anal. Calcd for $C_{22}H_{30}O_4NCl$: C, 64.77; H, 7.41; N, 3.43. Found: C, 64.65; H, 7.45; N, 3.48.

(5R,9R,13R,14S)-14-Chloromethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Ethyleneacetal (4c)

Synthesis of **4c** was carried out as described for **4a** with addition of 0.5 ml of abs. ethylene glycol instead of methanol. Colorless oil (780mg, 62 %).

^{1}H-nmr [$CDCl_3$] δ 6.78, 6.65 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 4.97 (dd, 1H, J = 3 Hz, J = 10 Hz, 8a-H), 4.53 (s, 1H, 5-H), 3.93 (s, 3H, arom.OCH_3), 3.99 - 3.86 (m, 2H, 2H, -O-CH_2-CH_2-O-), 2.39 (s, 3H, NCH_3); ms (m/z) 377/379 (M^+).

(5R,9R,13S,14R)-4,5-Epoxy-3,6,6-trimethoxy-14,17-methano-17-methyl-C-normorphinanium Perchlorate (5a)

A solution of **4a** (80 mg, 0.21 mM) in 5 ml of methanol and 3 drops of 2N ammonia was heated under reflux over a period of 3 h. The mixture was then evaporated, the residue was dissolved in dichloromethane and extracted with water. The aqueous layer was evaporated and redissolved in 2N HCl. After addition of sodium perchlorate yellow crystals of **5a** (50 mg, 54 %) were formed. Recrystallization from water: mp 241 °C. ^{1}H-nmr [$CDCl_3$] δ 6.86, 6.77 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 5.11 (d, 1H, J = 9 Hz, H-8a), 4.73 (s, 1H, 5-H), 4.56 (d, 1H, J = 9 Hz, H-8b), 3.93 (s, 3H, arom. OCH_3), 3.59 (s, 3H, N^+-CH_3), 3.33, 3.19 (s,s, 3H, 3H, acetal-OCH_3), 2.53 (d, 1H, J = 14 Hz, 7β-H), 1.13 (d, 1H, J = 14 Hz, 7α-H). Anal. Calcd. for $C_{20}H_{26}NO_8Cl$: C, 54.11; H, 5.90; N, 3.15. Found: C, 53.67; H, 5.84; N, 3.14.

(4aR,10bS,11R)-10,11-Epoxy-9-methoxy-3-methyl-1,2,3,4-tetrahydro-4a,10b-propano-benzo[f]isoquinolin-12-one Dimethylacetal (6)

To a solution of 2 g of potassium hydroxide in 30 ml of methanol was added 380 mg (1 mM) of **4a**. The mixture was refluxed for 24 h. After addition of water the solution was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue gave 340 mg (100 %) of **6** as yellowish crystals (crystallization from methanol): mp 163 °C. ^{1}H-nmr [$CDCl_3$] δ 6.61, 6.56 (AB-system, 2H, J = 6 Hz,7-H, 8-H), 6.42 (d, J = 9.6 Hz, 6-H), 5.62 (d, J = 9.6 Hz, 5-H), 4.76 (s, 1H, 11-H), 3.85 (s, 3H, arom. OCH_3), 3.22, 3.19 (s,s, 3H, 3H, acetal-OCH_3), 2.29 (s, 3H, N-CH_3); ^{13}C-nmr [$CDCl_3$] δ 146.0 (10-C), 136.2 (6-C), 134.8 (9-C), 130.5 (10a-C), 124.9 (6a-C), 124.5 (5-C), 117.7 (7-C), 113.35 (8-C), 109.1 (12-C), 94.2 (11-C), 62.2, 51.6 (2-C and 4-C), 56.4 (arom.$O\underline{C}H_3$), 50.5, 48.7, 46.7 (acetal-$O\underline{C}H_3$, $N\underline{C}H_3$), 43.3, 42.1, 29.0, 28.6 (1-C, 4a-C, 10b-C and 13-C); ms (m/z) 343 (M^+). Anal. Calcd. for $C_{20}H_{25}O_4N$: C,69.94; H, 7.34; N, 4.08. Found: C, 69.69; H, 7.31; N, 3.88.

(5R,9R,13R,14S)-14-Bromomethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Dimethylacetal (7a)

Synthesis of **7a** was carried out as described for **4a**. Reagent: phosphorus tribromide (addition of 3 ml, 32 mM). White crystals (**7a**, 1.39 g, 97 %) from methanol: mp 135 - 137 °C. ^{1}H-nmr [$CDCl_3$] δ 6.70, 6.58 (AB-system, 2H, J = 8 Hz, 1-H, 2-H), 4.85 (dd, 1H, J = 2.5 Hz, J = 9 Hz, 8a-H), 4.50 (s, 1H, 5-H), 3.86 (s, 3H, arom. OCH_3), 3.75 (d, 1H, J = 9 Hz, 8b-H), 3.27, 3.25 (s, s, 3H, 3H, acetal-OCH_3), 2.37 (s, 3H, N-CH_3), 2.22 (d, 1H, J = 12.5 Hz, 7β-H), 0.99 (dd, 1H, J = 2.5 Hz, J = 12.5 Hz, 7α-H); ^{13}C-nmr [$CDCl_3$] δ 146.0 (4-C), 142.9 (3-C), 131.9 (12-C), 127.8 (11-C), 118.9 (1-C), 114.8 (2-C), 110.1 (6-C), 94.1 (5-C), 58.8, 57.0 (9-C and 18-C), 52.4, 45.5 (C-13 and C-14), 50.8, 49.7 (acetal-C), 45.7 (16-C), 43.5 (C-17), 40.7, 39.3 (7-C and 8-C), 27.8, 20.9 (10-C and 15-C); ms (m/z) 423/425 (M^+). Anal. Calcd. for $C_{20}H_{26}O_4NBr$ C, 56.61; H, 6.17; N, 3.30. Found: C, 56.57; H, 6.14; N, 3.29.

(5R,9R,13R,14S)-14-Bromomethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Diethylacetal (7b)

Synthesis of **7b** was carried out as described for **4b**. Reagent: phosphorus tribromide (addition of 3 ml, 32 mM), alcohol: ethanol (5 ml). Colorless oil (**7b**, 1.33 g, 89 %). ^{1}H-nmr [$CDCl_3$] δ 6.93, 6.79 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 5.03 (dd, 1H, J = 3 Hz, J = 10 Hz, 8a-H), 4.63 (s, 1H, 5-H), 3.94 (s, 3H, arom. OCH_3), 3.56 - 2.99 (q,q, 2H, 2H, acetal-CH_2-), 2.39 (s, 3H, N-CH_3), 1.16, 0.99 (t,t, 3H, 3H, J = 7.5 Hz, acetal-CH_3); ms (m/z) 451/453 (M^+).

(5R,9R,13R,14S)-14-Bromomethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Ethyleneacetal (7c)

Synthesis of **7c** was carried out as described for **4c**. Reagent: phosphorus tribromide (addition of 3 ml, 32 mM), alcohol: ethylene glycol (0.5 ml). Colorless oil (**7c**, 885 mg, 62 %). ^{1}H-nmr [$CDCl_3$] δ 6.73, 6.63

(AB-system, 2H, J = 9 Hz, 1-H, 2-H), 4.89 (dd, 1H, J = 3 Hz, J = 9 Hz, 8a-H), 4.37 (s, 1H, 5-H), 3.93 (s, 3H, OCH_3), 3.99 - 3.86 (m, 2H, 2H, acetal-CH_2-CH_2-), 2.39 (s, 3H, N-CH_3); ms (m/z) 421/423 (M^+).

(5R,9R,13R,14S)-14-Iodomethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Dimethylacetal (8a).

A solution of phosphorus triiodide (6.0 g, 15 mM) in dichloromethane was slowly added to a solution of 1 (300 mg, 1 mM) in 30 mL of dry dichloromethane and 5 ml of abs.methanol. The addition was carried out under N_2 and at -20 °C. The cooling bath was then removed and the mixture was stirred for 2 h. The reaction mixture was then poured into a solution of sodium bicarbonate in 200 ml of water. Extraction with dichloromethane gave yellowish crystals after drying over Na_2SO_4. Recrystallization from methanol afforded 470 mg **8a** (99 %): 131 - 132 °C. ^{1}H-nmr [$CDCl_3$] δ 6.76, 6.63 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 4.70 (dd, 1H, J = 3 Hz, J = 9Hz, 8a-H), 4.56 (s, 1H, 5-H), 3.90 (s, 3H, arom. OCH_3), 3.33, 3.26 (s,s, 3H, 3H, acetal-OCH_3), 2.40 (s, 3H, N-CH_3), 1.02 (dd, 1H, J = 3 Hz, J = 13.5 Hz, 7α-H); ms (m/z) 471 (M^+). Anal. Calcd. for $C_{20}H_{26}O_4NI$: C, 50.96; H, 5.56; N, 2.97. Found: C, 50.94; H, 5.55; N, 2.97.

(5R,9R,13R,14S)-14-Iodomethyl-4,5-epoxy-3-methoxy-17-methyl-C-nor-morphinan-6-one Diethylacetal (8b)

Synthesis of **8b** was carried out as described for **8a** with addition of 5 ml of abs. ethanol instead of methanol. White crystals from ethanol (8b, 470 mg, 93 %): 165 - 167 °C.

^{1}H-nmr [$CDCl_3$] δ 6.69, 6.57 (AB-system, 2H, J = 9 Hz, 1-H, 2-H), 4.69 (dd, 1H, J = 3 Hz, J = 9 Hz, 8a-H), 4.56 (s, 1H, 5-H), 3.90 (s, 3H, arom. OCH_3), 3.74 (d, 1H, 8b-H), 3.8 - 3.0 (q,q, 2H, 2H, acetal-CH_2-), 2.39 (s, 3H, N-CH_3), 1.22, 1.08 (t,t, 3H, 3H, J = 7 Hz, acetal-CH_3); ms (m/z) 499 (M^+). Anal. Calcd. for $C_{22}H_{30}O_4NI$: C, 52.91; H, 6.05; N, 2.80. Found: C, 52.90; H, 6.05; N, 2.80.

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Received, 15th June, 1987