213. The Oxidation of Thebaine with *m*-Chloroperbenzoic Acid. Studies in the (+)-Morphinan Series. III¹)²)

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Dedicated to Prof. *C. A. Grob* on the occasion of his sixtieth birthday

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Zur Oxydation von Thebain mit *m*-Chlorperbenzoesäure, III

Zusammenfassung

Die Oxydation von Thebain (**1**) mit *m*-Chlorperbenzoesäure ist stark abhängig von den gewählten Reaktionsbedingungen. In unserem Fall wird neben 14-Hydroxycodeinon (**2**) auch das bekannte, mono-acetylierte Diol **3** erhalten. Die Rückführung von **3** in **2** und die Verknüpfung mit dem bekannten Ketodiol **5**, über das bisher nicht beschriebene 8,14-Dihydroxydihydrothebain (**4**) wird gezeigt.

The procedure for the oxidation of thebaine (**1**) with *m*-chloroperbenzoic acid in a mixture of acetic and trifluoroacetic acid reported by *Hauser et al.* [1] is in our experience rather sensitive to small changes in the reaction conditions. Using shorter reaction times affords, after extraction of the basified solution with chloroform and crystallization from ethanol, the unsaturated ketone **2**, however in only 24% yield instead of the reported 74%. From the mother liquor of **2** the *O*-acetylated *cis*-diol **3** can be obtained in 36% yield after further concentration and standing at room temperature. The latter is very probably identical with material prepared by *Vieböck* during the oxidation of thebaine (**1**) with manganic acetate [2]. Conversion of **3** into **2** can readily be accomplished by treatment with a mixture of acetic and trifluoroacetic acid. Alkaline hydrolysis of **3** on the other hand affords the heretofore unknown *cis*-diol **4**. This is cleaved with hydrochloric acid to the keto-diol **5**, prepared by *Weiss* during the base catalysed hydration of 14-hydroxymorphinone [3]; a congener was prepared from acetylneopine by *Sargent et al.* [4] following treatment with osmium tetroxide. It is reasonable to assume that the formation of **3** originates from the hypothetical 8,14-β-epoxide of dihydrothebaine. Opening of the hypothetical

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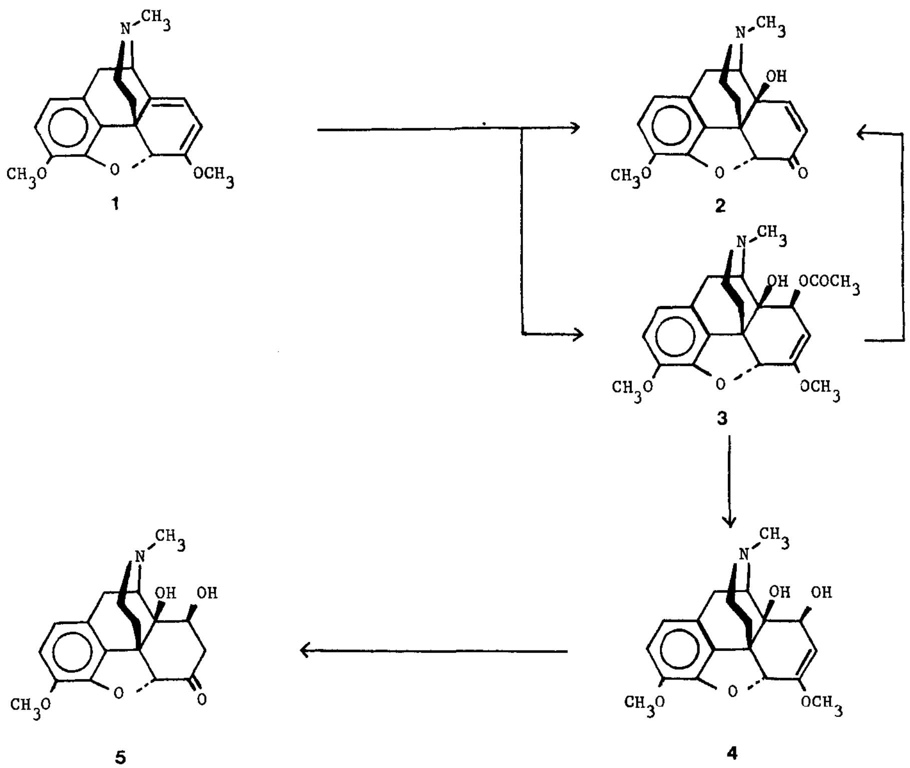
¹) Part II: *Y. F. Jacquet, W. A. Klee, K. C. Rice, I. Iijima & J. Minamikawa*, Science, in press, 1977.

²) These model studies in the (−)-series were initiated to find the best experimental conditions for preparing 14-hydroxymorphinans of the (+)-series.

epoxide ring with acetate in a *S_N1*-type reaction should be favored from the much less hindered β-side and afford the compounds described below with their correct configuration.



Experimental part

Melting points were determined on a *Thomas-Hoover* melting point apparatus and are corrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this Laboratory. IR., NMR. and mass spectra were obtained on a *Perkin-Elmer* 257, a *Varian* Model A-60A and a *Hitachi* RMU-6E (70 eV), respectively. Optical rotations were measured with *Perkin-Elmer* Model 141 Polarimeter.

Oxidation of thebaine with m-*chloroperbenzoic acid.* To a stirred solution of 10.0 g of thebaine (**1**) in 40 ml of acetic acid and 5.3 g of trifluoroacetic acid was added 4.41 g of *m*-chloroperbenzoic acid over 5 min. After heating for 5 min at 95° (bath temperature) 3.12 g of additional *m*-chloroperbenzoic acid was added over 5 min. Following the second addition, the mixture was heated for 10 min at 90° and stirred for an additional 10 min at RT., cooled and then poured into 150 ml of ice/water. After stirring for 30 min, the solid was filtered off and washed with water. The filtrate was made basic with NH_3-solution, extracted with chloroform, the organic solution was washed with water and then dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was crystallized from ethanol to afford 2.44 g (24.3%) of 14-hydroxycodeinone (**2**), m.p. 274–275°, $[\alpha]_D^{20} = -109.3°$ ($c = 1$, 10% AcOH) (lit. [1]: m.p. 275°; lit. [5]: $[\alpha]_D^{25} = -111°$ in 10% AcOH). From the mother liquor of **2**, 4.53 g (36.5%) of 8-acetoxy-14-hydroxydihydrothebaine (**3**), m.p. 196°, $[\alpha]_D^{20} = -192.7°$ ($c = 0.99$, $CHCl_3$) (lit. [2]: m.p. 196–198°), was obtained after further concentration and standing at RT.

Conversion of 8-acetoxy-14-hydroxydihydrothebaine (**3**) *to 14-hydroxycodeinone* (**2**). A mixture of 300 mg of **3**, 0.2 ml of trifluoroacetic acid and 1 ml of acetic acid was heated at 100° for 1 h and evaporated under reduced pressure. The residue was dissolved in water, made basic with NH_3-solution, the solid formed was filtered off, washed with water, 95% ethanol and ether. Recrystallization from ethanol containing a small amount of chloroform gave 198 mg (81.6%) of **2**, m.p. 274–275°.

8,14-Dihydroxydihydrothebaine (**4**). A mixture of 500 mg of **3**, 10 ml of 10% NaOH-solution and 10 ml of ethanol was heated on a steam bath for 1 h and concentrated under reduced pressure. The residue was extracted with $CHCl_3$, the extracts were washed with saturated NaCl-solution and then dried over $MgSO_4$. Evaporation of the solvent afforded a solid, which was recrystallized from ethanol to give 324 mg (72.7%) of **4**, m.p. 197–198°; $[\alpha]_D^{20} = -198.0°$ ($c = 1$, EtOH). – IR. ($CHCl_3$): 3520, 3350, 1660, 1645, 1608 cm^{-1}. – NMR. ($CDCl_3$): 2.42 (*s*, 3 H, N–CH_3); 3.53 (*s*, 3 H, CH_3O–C(6)); 3.83 (*s*, 3 H, CH_3O–C(3)); 4.71 (*d*, 1 H, H–C(7) or H–C(5)); 4.85 (*d*, 1 H, H–C(5) or H–C(7)); 6.68. – MS.: 345 (M^+, 100) 330 (18) 312 (33) 302 (22).

$C_{19}H_{23}NO_5$ (345.38) Calc. C 66.07 H 6.71 N 4.05% Found C 66.03 H 6.66 N 4.10%

8,14-Dihydroxydihydrocodeinone (**5**). A mixture of 900 mg of **4** and 10 ml of 5% HCl-solution was heated at 80° (bath temperature) for 15 min. After cooling in an ice bath, colorless needles which formed were filtered off, washed with a small amount of cold water and dried to afford 845 mg (88%) of **5** · HCl, m.p. 253° (dec.) [lit. [3]: m.p. 260° (dec.)]. Base (**5**), m.p. 169–170°, $[\alpha]_D^{20} = -191.5°$ ($c = 1$, 95% EtOH), (lit. [4]: m.p. 169–170°, $[\alpha]_D^{20} = -191°$ (95% EtOH), (lit. [3]: m.p. 173°) was obtained by treatment of **5** · HCl with ammonium hydroxide and recrystallization from very dilute ethanol. The product was identified by mixed m.p. and by comparison of its IR., NMR. and mass spectra with those of an authentic sample prepared by the method of *Vieböck*.

We wish to thank Dr. *U. Weiss* of our Institute for a sample of 8,14-dihydroxydihydrocodeinone (**5**) prepared by reaction of diazomethane with the corresponding morphinone derivative as previously described [3].

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