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A Stereohomogeneous Synthesis of N-Demethyl-N-Substituted-14-Hydroxydihydromorphines**

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Summary. A new route for the stereohomogeneous synthesis of N-demethyl-N-substituted-14-hydroxydihydromorphines **2a–f** has been elaborated, involving O-demethylation of the novel dihydrocodeine derivatives **6a–f**, obtained upon alkylation of the hitherto unknown N-demethyl-14-hydroxydihydrocodeine (**5**).

Keywords. 6α,14β-Diacetoxy-4,5α-epoxy-3-methoxy-17-methyl-morphinan, N-demethylation of; 3,6α,14β-Triacetoxy-17-alkyl-4,5α-epoxymorphinan, N-demethylation of; 17-Alkyl-4,5α-epoxy-6α-,14β-dihydroxy-3-methoxymorphinan, O-demethylation of; 4,5α-Epoxy-6α,14β-dihydroxy-3-methoxymorphinan, N-alkylation of.

Synthese von N-Demethyl-N-Substituierten-14-Hydroxydihydromorphinen in stereochemisch einheitlicher Form

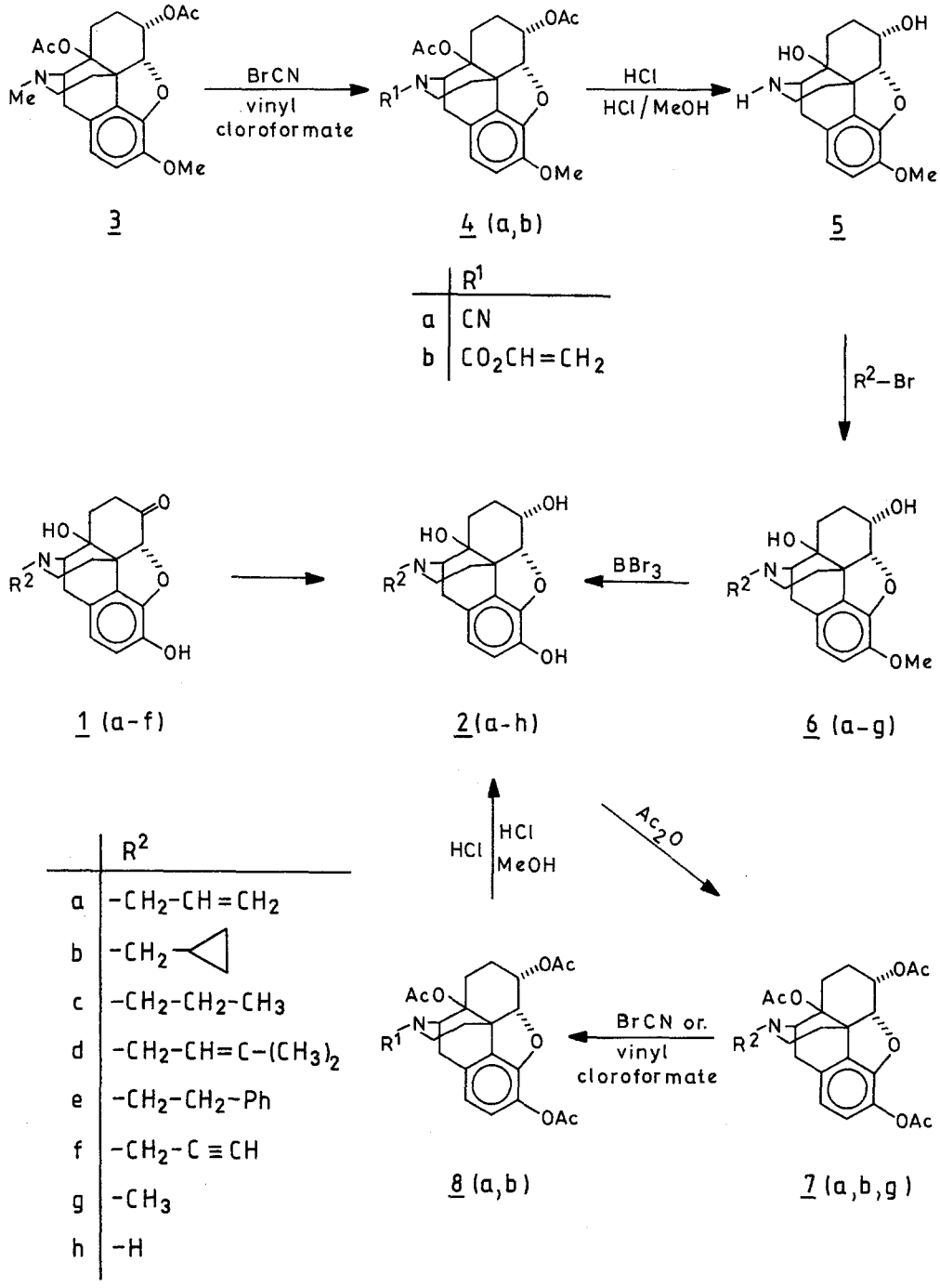
Zusammenfassung. Es wurde ein neuer Weg für die Darstellung von N-Demethyl-N-Substituierten-14-Hydroxydihydromorphinen **2a–f** in stereochemisch einheitlicher Form ausgearbeitet. Diese erfolgte durch die O-Demethylierung der neuen Dihydrocodein-Derivate **6a–f**, die durch N-Alkylierung des neuen N-Demethyl-14-hydroxycodeins hergestellt wurden.

Introduction

N-Demethyl-N-substituted-14-hydroxydihydromorphines **2a–f** are pharmaceutically important substances due to their simultaneous agonist and antagonist properties, and because the type of effect of such derivatives on various opiate receptors (μ, χ, σ) is still not completely understood [2]. Moreover, of these compounds α-Naloxol (**2a**) and α-Naltrexol (**2b**) have been identified among the metabolites of Naloxon (**1a**) and Naltrexon (**1b**), respectively.

** Dedicated to Prof. Dr. W. Fleischhacker on the occasion of his 60th birthday

Reported synthetic routes [3, 4] to the title compounds **2a–f** involve the reduction of the corresponding 6-oxo derivatives **1a–f** with sodium borohydride in ethanol or methanol, but this method does not lead to stereochemically homogeneous products: besides the so-called α-isomers (C_6-OH: α), 5–10% of the β-isomer (C_6-OH: β) were also produced. Separation of these diastereoisomers (epimers) could only be achieved [5, 6] by repeated recrystallization, or by means of tedious chromatographic techniques.



Results and Discussion

Reduction of the oxo-compounds **1a–f** with various reducing agents in different solvents (with sodium borohydride in ethanol, tetrahydrofuran and dioxane, with lithium aluminum hydride in tetrahydrofuran, or with aluminum propoxide) resulted in mixtures of epimers containing 5–10% of the β-isomer. Therefore, a new strategy was elaborated for the synthesis of the pure α-diastereoisomers, involving the preparation of the hitherto unknown N-demethyl-14-hydroxydihydrocodeine (**5**) in stereochemically homogeneous form by means of acetylation of the readily available [7] 14-hydroxydihydrocodeine (**6g**), followed by N-demethylation of the produced 6α,14β-diacetate **3** in two different ways. Thus, first the cyanamide **4a**, obtained upon treatment with cyanogene bromide, was subjected to aqueous-acid hydrolysis to give the N-demethyl derivative **5**. Following the other method [8], the carbamate **4b**, prepared by the addition of vinyl chloroformate, was sequentially treated with dry hydrochloric acid gas and methanol yielding the N-demethyl compound **5**. By means of the alkylation of this latter several new N-alkyl derivatives **6a–f** could be prepared, which were converted into the desired 14-hydroxydihydromorphines **2a–f** by O-demethylation with boron tribromide.

The synthesis of the hitherto unknown N-demethyl-14-hydroxydihydromorphine (**2h**) could also be achieved by the N-demethylation of the triacetate **7g** – obtainable by the acetylation of 14-hydroxydihydromorphine (**2g**) – with cyanogen bromide or vinyl chloroformate. Hydrolysis of the cyanamide **8a** and the carbamate **8b** was performed as described above.

We have also prepared the 3,6,14-triacetates **7a** and **7b** of α-Naloxol (**2a**) and α-Naltrexol (**7b**). These compounds were previously reported [9] as non-crystalline, extremely unstable substances. We have succeeded in the isolation of both of these derivatives in pure crystalline form by means of column chromatography.

The ^{1}H-NMR spectra of these compounds (Table 1) showed the following characteristic features: the C_6-O-acetyl-methyl signal appeared below 2.0 ppm, as a result of the favoured geometrical arrangement of the aromatic ring and the 6-O-acetyl group to cause a diamagnetic anisotropic effect [10]. In addition, due to acetylation of the 14-hydroxy group the signal of 9αH suffered a downfield shift ($\delta = 4.2$ ppm) of an easily interpretable diagnostic value.

Experimental

N-Demethylation with Cyanogen Bromide

To a solution of the N-methyl compound (7 mmol) in dry chloroform (40 ml) a solution of cyanogen bromide (1.5 g, 14 mmol) in chloroform (20 ml) was added and the mixture was refluxed at 60°C for 8 h. Then a second volume (1.5 g, 14 mmol) of cyanogen bromide in 20 ml of chloroform was added and reflux was continued for another 8 h. The reaction mixture was evaporated to dryness in vacuo, the residue was dissolved in chloroform (100 ml) and washed with 1% aq. hydrochloric acid and water and then dried (magnesium sulfate). After evaporation the residual solid crude cyanamide was suspended in a tenfold excess of 10% aq. hydrochloric acid and refluxed for 16 h with stirring under nitrogen atmosphere. After cooling the precipitated crystalline hydrochloride salt of the N-demethyl derivative was isolated by filtration. The free base was obtained upon treatment of an aqueous solution of the salt with 25% ammonium hydroxide.

Table 1. Physical constants and characteristic ^{1}H-NMR data (in $CDCl_3$ if not otherwise stated)

Compd.	M. p. (°C) solvent	Yield (%)	Molecular formular[a]	^{1}H-NMR (ppm)
2a	200-202 methanol	62	$C_{19}H_{23}NO_4$	4.1 – 4.4 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H), 4.85 – 5.3 (m, allyl), 6.5 – 6.6 (dd, 2 H, *Ar*)
2b	169 – 171 acetone	85	$C_{20}H_{25}NO_4$	0.5 – 1.8 (m, cyclopropyl), 4.3 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H)
2c[b]	234 – 236 ethanol	65	$C_{19}H_{25}NO_4$	0.95 (m, 3 h, *Me*), 4.0 (m, 1 H, 6β-H), 4.5 (d, 1 H, 5β-H), 6.5 (dd, 2 H, *Ar*)
2d	oil	37	$C_{21}H_{27}NO_4$	1.6 – 1.7 (s, 6 H, *Me*), 4.2 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H), 5.1 (m, 1 H, allyl)
2e	245 – 247 ethanol	63	$C_{24}H_{27}NO_4$	4.2 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H), 6.65 (dd, 2 H, *Ar*), 7.25 (m, 5 H, *Ar*)
2f	256 – 257 ethanol	42	$C_{19}H_{21}NO_4$	3.4 (d, 2 H, N-CH_2-), 4.2 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H), 6.6 (dd, 2 H, *Ar*)
2h[b]	257 – 259 ethanol	60	$C_{16}H_{19}NO_4$	4.1 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H), 6.6 – 6.7 (dd, 2 H, *Ar*)
4a	222 – 224 ethanol chloroform	95	$C_{22}H_{24}N_2O_6$	1.8 (s, 3 H, 6-O*Ac*), 2.25 (s, 3 H, 14-O*Ac*), 3.85 (s, 3 H, O*Me*), 4.6 (d, 1 H, 5β-H), 5.4 (m, 1 H, 6β-H), 6.6 – 6.7 (dd, 2 H, *Ar*)
4b	146 – 147 methanol	70	$C_{24}H_{27}NO_8$	1.85 (d, 3 H, 6-O*Ac*), 2.05 (d, 3 H, 14-O*Ac*), 3.85 (s, 3 H, O*Me*), 4.7 (m, 1 H, 5β-H), 5.3 (m, 1 H, 6β-H), 6.6 – 6.7 (dd, 2 H, *Ar*)
5[b]	212 – 214 ethanol	70	$C_{17}H_{21}NO_4$	3.8 (s, 3 H, O*Me*), 4.4 (d, 1 H, 5β-H), 6.5 – 6.7 (dd, 2 H, *Ar*)
6a	140 – 142 ethanol	71	$C_{20}H_{25}NO_4$	3.8 (s, 3 H, O*Me*), 4.7 (d, 1 H, 5β-H), 5.2 (m, 3 H, allyl), 6.6 – 6.7 (dd, 2 H, *Ar*)
6b	143 – 145 ethanol	63	$C_{21}H_{27}NO_4$	0.2-1.8 (m, cyclopropyl), 3.85 (s, 3 H, O*Me*), 4.23 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H)
6c	94 – 96 ethanol	56	$C_{20}H_{27}NO_4$	0.95 (t, 3 H, *Me*), 3.85 (s, 3 H, O*Me*), 4.2 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H)
6d	oil	48	$C_{23}H_{29}NO_4$	1.6 – 1.7 (s, 6 H, Me), 3.9 (s, 3 H, O*Me*), 4.2 (m, 1 H, 6β-H), 4.6 (d, 1 H, 5β-H), 5.2 (m, 1 H, allyl), 6.65 (dd, 2 H, *Ar*)
6e	134 ethanol	56	$C_{25}H_{29}NO_4$	3.85 (s, 3 H, O*Me*), 4.6 (d, 1 H, 5β-H), 6.65 (dd, 2 H, *Ar*), 7.3 (m, 5 H, *Ar*)
6f	142 – 143 ethanol	54	$C_{20}H_{23}NO_4$	3.4 (d, 2 H, N-CH_2-), 3.85 (s, 3 H, O*Me*), 4.65 (d, 2 H, 5β-H and 14-OH)

7a	107–110 ethanol	53	$C_{25}H_{29}NO_7$	1.95 (s, 3H, 6-O*Ac*), 2.1 (s, 3H, 14-O*Ac*), 2.3 (s, 3H, 3-O*Ac*), 4.8 (d, 1H, 5β-H), 5.2 (m, 3H, allyl and 6β-H)
7b	119–122 ethanol	48	$C_{26}H_{31}NO_7$	1.95 (s, 3H, 6-O*Ac*), 2.1 (s, 3H, 14-O*Ac*), 2.3 (s, 3H, 3-O*Ac*), 4.8 (d, 1H, 5β-H), 4.8 (d, 1H, 6β-H), 6.7 (dd, 2H, *Ar*)
8a	196–198 ethanol	86	$C_{23}H_{24}N_2O_7$	1.9 (s, 3H, 6-O*Ac*), 2.2 (s, 3H, 14-O*Ac*), 2.3 (s, 3H, 3-O*Ac*), 4.7 (d, 1H, 5β-H), 5.8 (m, 1H, 6β-H), 6.8 (dd, 2H, *Ar*)
8b	237–239 methanol	40	$C_{25}H_{27}NO_9$	1.95 (s, 3H, 6-O*Ac*), 2.2 (s, 3H, 14-O*Ac*), 2.3 (s, 3H, 3-O*Ac*), 4.6 (m, 1H, 5β-H), 5.3 (m, 1H, 6β-H), 6.6 (dd, 2H, *Ar*)

[a] All compounds gave acceptable elemental analysis

[b] ^{1}H-NMR in *DMSO-d_6*

N-Demethylation with Vinyl Chloroformate

According to the method of Olofson [8] a solution of the N-methyl derivative in 1,2-dichloroethane was reacted with vinyl chloroformate in the presence of sodium hydrogen carbonate. Then a dichloromethane solution of the urethane derivative was treated with hydrochloric acid gas for 1 h, the solution was evaporated to dryness and the residue was heated with a 1 : 1 mixture of hydrochloric acid and water when the deacetylated derivative of the hydrochloride salt was separated in crystalline form.

N-Alkylation

A stirred suspension of the N-demethyl derivative (5.0 mmol), sodium hydrogen carbonate (0.7 g) and the alkyl halogenide (6.0 mmol) in ethanol (50 ml) was heated at 70°C for 20 h. After cooling the inorganic salt was removed by filtration, the filtrate was evaporated and the residue was taken up with chlorofom. The insoluble substances were filtered off and the filtrate was concentrated. In the case of allylation (**6a**) the product was obtained in pure form, whereas upon dimethylallylation (**6d**) and propargylation (**6f**) purification was carried out by means of column chromatography (silicagel, 9 : 1 chloroform-methanol). For cyclopropyl-methylation (**6b**) and β-phenylethylation (**6e**) ethanol was replaced with N,N-dimethylformamide. Followed by evaporation the residue was dissolved in water (100 ml) and this aqueous solution was extracted with chloroform (3 × 30 ml). The combined organic extracts were washed with aq. sodium chloride, dried and concentrated. The crude product was crystallized from ethanol.

O-Demethylation

To a cold (0°C) solution of boron tribromide (1.2 ml, 12 mmol) in dry chloroform (50 ml) a solution of the codeine derivative (5.8 mmol) in chloroform (30 ml) was dropwise added over a period of 20 min with stirring and under nitrogen atmosphere. Stirring was continued for 60 min at 0 − 5°C and then the mixture was poured onto ice (100 g) and the *pH* of the aqueous layer was adjusted to 8.5 − 9.0 by the addition of aq. ammonium hydroxide. The chloroform layer was separated and the aqueous phase was extracted with chloroform (3 × 20 ml). The combined organic extract were washed with aq. sodium chloride, dried and concentratcd.

Preparation of the Triacetates

The hydroxy derivatives (0.1 g) were treated with acetic anhydride (3.0 ml) at 100°C for 1 h. The excess of the reagent was removed by evaporation in vacuo and the products were converted into the free bases.

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