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Synthesis of N-Demethyl-N-Substituted-14-Hydroxycodeine and Morphine Derivatives+

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A fews representatives (1b-d) of a novel group of structurally related morphine-antagonist compounds have been prepared in stereochemically homogeneous form. The employed procedures involve O-demethylation either of the corresponding codeine derivatives 2b-d, or those of the N-alkylated analogues 2b,c, synthesized from N-demethylthebaine (7a) by means of N-alkylation and subsequent transformations of 7b,d, - compounds selected from the resulting functionalized thebaines 7b-e.

Our ongoing research program, aimed at the synthesis of morphine-antagonist compounds and at the examination of the

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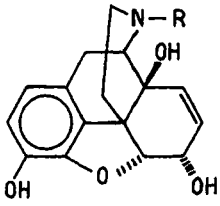
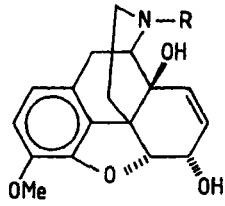
agonist/antagonist properties of these derivatives - permitting the recognition of fine details of the structure-activity relationship - requires the pharmacological examination of a great number of structurally related derivatives belonging to certain groups of stereochemically homogeneous morphine alkaloids.

In the frame of this program we have previously reported the synthesis of N-demethyl-N-substituted isocodeine and isomorphine[1], N-demethyl-N-substituted-dihydroisocodeine and -dihydroisomorphine[2], as well as the preparation of N-demethyl-N--substituted 14-hydroxy-dihydrocodeine- and -dihydromorphine derivatives[3].

In the present paper the synthesis of N-demethyl-N-substituted 14-hydroxycodeine and 14-hydroxymorphine derivatives is described. Of the morphine substances only the base compound 14-hydroxymorphine (1a)[4] and its N-demethyl-N-(cyclopropylmethyl) derivative (1b)[5] have been previously known in the literature.

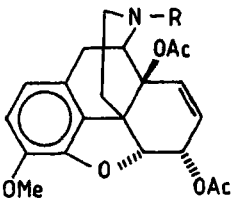
Based on the recognition that functionalized morphine derivatives can be most conveniently prepared by means of the O-demethylation of the corresponding codeine analogues, two possibilities were studied for obtaining these latter compounds. First, N-demethylation of 14-hydroxycodeine (2a) was investigated, and as the second approach, the N-substituted derivatives of 2e were synthesized from the N-demethyl-N-alkyl-thebaines 7a-e.

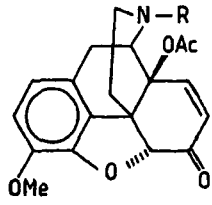




1a R = Me	2a R = Me	e R = H
b R = CPM	b R = CPM	f R = Ac
c R = nPr	c R = nPr	g R = CH_2CH_2Ph
d R = $CH_2CH{=}CH_2$	d R = $CH_2CH{=}CH_2$	h R = CH_2-◇

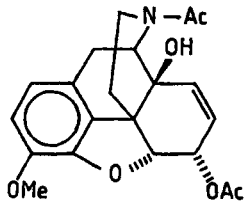
N-Demethyl-14-hydroxycodeine (2e) has been prepared earlier by Currie et al[6]; the von Braun reaction of 14-hydroxycodeine diacetate (3a) gave the cyanamide 3b, which was subjected to reduction with lithium aluminium hydride in ether (for 66 hrs) to obtain 2e. We observed that this reaction was completed over 8-10 hrs reaction time, whereupon the solvent was changed to tetrahydrofuran. The mild acid hydrolysis of 3b (6 % aqueous HCl) led to an unexpected extensive decomposition.



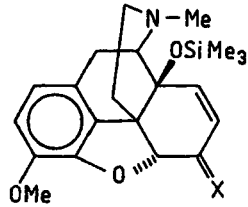


3a R = Me	4a R = Me
b R = CN	b R = CN
c R = $CO_2CH{=}CH_2$	
d R = Ac	

From the preparative point of view 2a is more readily available by means of the reduction ($LiAlH_4$-THF) of the cyanamide 4b, accessible from 14-O-acetylcodeinone (4a). Studies on the N-demethylation of 14-hydroxycodeine with vinyl chloroformate[7-9] revealed that 3a can be conveniently transformed into the readily crystallizable vinylurethane 3c. Then degradation of the vinylurethane unit in a two-step sequence (1. hydrochloric acid addition; 2. reflux in methanol) afforded the hydrochloride salt of the 6,14-diacetate of 2e. Upon treatment of this latter with 10 % aqueous sodium hydrogen carbonate the N-acetyl derivative 5 (produced by O ⟶ N acetyl-migration) was isolated. Acid hydrolysis of the diacetate in 10 % hydrochloric acid, to give 2e, could be effected only with a moderate yield, because of extensive decomposition.



5



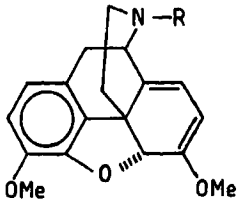
6a X = O
b X = OH

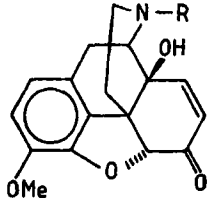
This O ⟶ N acetyl-migration (3b 5) has also been observed by Currie and his coworkers[6]. By the acetylation of 5 we obtained the triacetate of N-demethyl-14-hydroxycodeine (3d).

In the ^{1}H-NMR spectra of the N-acetyl derivatives 3d and 5 the "acetyl-methyl" protons appear in form of dublets, indicating the presence of rotamers.

To avoid the undesired O ⟶ N acetyl migration, mentioned above, the C-14 hydroxyl was temporarily protected by means of trimethylsilylation. Reduction of 14-trimethylsilyloxycodeinone (6a)[10] with sodium borohydride in methanol afforded 14-trimethylsilyl-oxycodeine (6b), which was reacted with vinyl chloroformate. The resulting vinylurethane was subjected to the usual degradation without isolation, to give directly 2e with simultaneous split-off the trimethylsilyl protecting group. It is to be noted that of the mentioned procedures the present one, detailed above, is to be considered as the most convenient route to 2e.

Subsequent N-alkylation (R-Br; DMF) of N-demethyl-14--hydroxycodeine (2e) readily afforded the N-propyl (2c) and N-allyl (2d) derivatives. Compound 2d could not be crystallized, but its diacetate is a highly crystalline substance.





7a R = H
b R = nPr
c R = CH_2CH_2Ph
d R = CH_2- 
e R = CH_2- 

8a R = nPr
b R = CH_2CH_2Ph
c R = CH_2- 
d R = CH_2-

Table 1

Physical constants of compounds

Compound	m.p. (°C) (solvent)	Yield (%)	Compound	m.p. (°C) (solvent)	Yield (%)
1b	225-227 (EtOH)	44	2d	oil	72
			2d-diacetate	158-160 (EtOH)	58
1c	192-193 (ether)	35			
			2g	129-130 (EtOH)	50
1c.HCl	243-244 (EtOH)				
1d	203-204 (EtOH)	36	2h*	oil	70
8b	148-149 (EtOH)	68	3c	153-155 (MeOH)	72
8d	oil	46	6b	148-150 (ether)	90
7c	123-124 (EtOH)	70	5	251-253 (MeOH) 249-250[6]	57
7c*	oil	66	3d	183-185 ($CHCl_3$-MeOH) 185-186[6]	72
2c	oil	64			

*after chromatographic separation

Table 2

Mass spectra and the caracteristic ^{1}H-NMR data of compounds

Compound	Mass spectrum	PMR (ppm) $CDCl_3$; or DMSO-d_6
1b	$C_{20}H_{23}NO_4$ (341.38) 341 (M^+; 27 %)	6.7-6.5 dd (H-1,2; 2H), 5.9 m (H-7; 1H), 5.5 m (H-8; 1H), 4.9 d (H-5; 1H), 4.7 m (H-6; 1H), 1.0-0.2 m (cyclopropyl protons)
1c	$C_{19}H_{23}NO_4$ (329.39) 329 (M^+; 34 %), 300 (63 %)	6.6-6.5 dd (H-1,2; 2H), 5.85 m (H-7; 1H), 5.5 m (H-8; 1H), 4.8 d (H-5; 1H), 4.65 m (H-6; 1H), 0.95 t ($CH_3CH_2CH_2$; 3H)
1d	$C_{19}H_{21}NO_3$ (327.37) 327 (M^+; 30 %)	6.65-6.5 dd (H-1,2; 2H), 6.9-6.8 m (H-7 and allyl proton; 2H), 6.5 m (H-8; 1H), 5.3-5.1 m (allyl protons; 2H), 5.85 d (H-5; 1H), 5.6 m (H-6; 1H)
8b	$C_{25}H_{25}NO_4$ (403.45) 403 (M^+; 3 %), 312 (100 %)	7.3-7.2 m (aromatic protons; 5H), 6.7-6.5 m (H-1,2 and H-8; 3H), 6.15 d (H-7; 1H), 4.7 s (H-5; 1H), 3.82 s (OMe; 3H)
8d	$C_{22}H_{25}NO_4$ (367.4) 367 (M^+; 10 %), 312 (40 %)	6.7-6.6 m (H-1,2 and H-8; 3H), 6.55 d (H-7; 1H), 4.7 s (H-5; 1H), 3.85 s (OMe; 3H)
7c	$C_{26}H_{27}NO_3$ (401.48) 401 (M^+; 58 %), 310 (43 %), 255 (67 %)	7.3-7.2 m (aromatic protons; 5H), 6.7-6.6 dd (H-1,2; 2H), 5.55 d (H-8; 1H), 5.3 s (H-5; 1H), 5.05 d (H-7; 1H), 3.85 s (3-OMe; 3H), 3.6 s (6-OMe; 3H)
7e	$C_{23}H_{27}NO_3$ (365.45) 365 (M^+; 2 %), 205 (5 %)	6.7-6.55 dd (H-1,2; 2H), 5.55 d (H-8; 1H), 5.3 s (H-5; 1H), 5.05

(continued)

Table 2 Continued

Compound	Mass spectrum	PMR (ppm) $CDCl_3$; or DMSO-d_6
		d (H-7; 1H), 3.85 s (3-OMe; 3H), 3.6 s (6-OMe; 3H)
2c	$C_{20}H_{25}NO_4$ (343.39) 343 (M^+; 15 %), 314 (27 %)	6.6 dd (H-1,2; 2H), 5.9 m (H-7; 1H), 5.5 m (H-8; 1H), 4.9 d (H-5; 1H), 4.6 m (H-6; 1H), 3.8 s (OMe; 3H), 0.95 t ($CH_3CH_2CH_2$; 3H)
2d	$C_{20}H_{23}NO_4$ (341.38) 341 (M^+; 8 %)	6.7-6.55 m (H-1,2; 2H), 6.0-5.7 m (H-7 and allyl proton; 2H), 5.5 m (H-8; 1H), 5.3-5.15 m (allyl protons; 2H), 5.9 d (H-5; 1H), 4.6 m (H-6; 1H)
2d-diacetate	$C_{24}H_{27}NO_6$ (425.46) 425 (M^+; 31 %), 382 (100 %)	6.7-6.5 dd (H-1,2, 2H), 6.0 m (H-7; 1H), 5.8-5.65 m (allyl protons; 2H), 5.4 m (H-8; 1H), 5.25-5.1 m (allyl proton; H-5; 2H), 4.2 d (H-9; 1H), 3.85 s (OMe; 3H), 2.15 s (14-OAc; 3H), 2.05 s (6-OAc; 3H)
2g	$C_{25}H_{27}NO_4$ (405.46) 314 (100 %), M^+ not detectable	7.4-7.2 m (aromatic protons; 5H), 6.7-6.5 dd (H-1,2; 2H), 5.9 m (H-7; 1H), 5.45 m (H-8; 1H), 4.85 d (H-5; 1H), 4.6 m (H-6; 1H), 3.8 s (OMe; 3H)
2h	$C_{22}H_{27}NO_4$ (369.45) 369 (M^+; 42 %), 314 (100 %)	6.7-6.5 dd (H-1,2; 2H), 5.9 m (H-7; 1H), 5.5 m (H-8; 1H), 4.85 d (H-5; 1H), 4.6 m (H-6; 1H), 3.8 s (OMe; 3H)
3c	$C_{24}H_{25}NO_8$ (455.48) 455 (M^+; 33 %), 395 (62 %)	7.3-7.2 m (vinyl proton; 1H), 6.75-6.55 dd (H-1,2; 2H), 6.1-6.0 m (H-7; 1H), 5.8 m (H-8; 1H),

Table 2 Continued

Compound	Mass spectrum	PMR (ppm) $CDCl_3$; or DMSO-d_6
		5.5-5.4 m (vinyl proton; H-6; 2H), 5.1 d (H-5; 1H), 4.9-4.8 m (vinyl proton; 1H), 4.5 d (H-9; 1H), 3.85 s (OMe; 3H), 2.15 s (14-OAc; 3H), 2.0 d (6-OAc; 3H)
6b	$C_{21}H_{29}NO_4Si$ (387.52) 387 (M^+; 18 %), 229 (100 %)	6.65-6.5 dd (H-1,2; 2H), 5.8-5.7 m (H-7; 1H), 5.55 m (H-8; 1H), 4.8 d (H-5; 1H), 4.5 m (H-6; 1H), 3.8 s (OMe; 3H), 2.3 s (N-Me; 3H), 0.1 s ($SiMe_3$; 9H)
5	$C_{21}H_{23}NO_6$ (385.4) 385 (M^+; 12 %), 308 (10 %)	6.70-6.55 dd (H-1,2; 2H), 5.8 m (H-7; 1H), 5.7 m (H-8; 1H), 5.5 m (H-6; 1H), 5.2 m (H-9; 1H), 5.1 d (H-5; 1H), 3.85 s (OMe; 3H), 2.2-2.1 d (N-acetyl; 3H), 2.1 s (OAc; 3H)
3d	$C_{23}H_{25}NO_7$ (427.44) 427 (M^+; 3 %), 367 (18 %), 308 (24 %)	6.7-6.55 dd (H-1,2; 2H), 6.1-5.8 m (H-7; H-8; H-9; 3H), 5.2 m (H-6; 1H), 5.1 d (H-5; 1H), 3.8 s (OMe; 1H), 2.15-1.97 m (acetyl protons; 9H)

By the N-alkylation of N-demethylthebaine (7a)[11] the N-demethyl-N-propyl (7b)[12], the -N-phenylethyl (7c) and the -N-(cyclopropylmethyl) (7d)[5] analogues of thebaine were synthesized. N-Demethyl-N-(cyclobutylmethyl)-thebaine (7e) was prepared by means of the acylation of 7a with cyclobutanecarbonyl chloride and subsequent reduction with lithium aluminium chloride in tetrahydrofuran. Treatment of compounds 7b-e with $HCOOH-H_2O_2$ gave rise to the 14-hydroxycodeinones 8a-d, and then reduction ($NaBH_4$-methanol) afforded the N-demethyl-N-alkyl-14-hydroxy-codeines 2b,c,g,h. O-Demethylation of the 14-hydroxycodeines 2b,c,d, carrying the so-called "antagonist" N-substituents, with boron tribromide allowed the isolation of the corresponding 14-hydroxymorphine derivatives 1b,c,d.

It is known that the presence of the C-14 hydroxyl group in the morphine skeleton advantageously influences the pharmacological properties. As compared to the corresponding 14-H-analogues, generally both the agonist and antagonist activities are increasing, but "pure" antagonist compounds are known[12] only in the series of the 14-hydroxy-substituted derivatives.

The results of pharmacological examination of the morphines 1a-d will be published separately in a forthcoming paper.

EXPERIMENTAL

Melting points were determined with an "Electrothermal" (8103) digital instrument in open capillary tubes, and the data are

uncorrected. For thin layer chromatography precoated Kieselgel 60 F_{254} (MERCK 5554) layer and a 8:2 benzene-methanol mixture were applied. Visualization of the chromatograms was carried out with the Dragendorff-reagent. For column chromatography Kieselgel 60 M adsorbent and 9:1 benzene-methanol and 9:1 chloroform-methanol eluents were applied. The ^{1}H-NMR- and mass spectra were obtained with Varian-Gemini 200 and VG-TRIO-2 spectrometers, respectively.

N-Alkylation methods (alkylation of 2e and 7a)

To a solution of 2e or 7a (10 mmol) in abs. N,N-dimethylformamide (15 ml) powdered sodium hydrogen carbonate (1.2 g) and the appropriate alkyl bromide (12 mmol) were added. After stirring at 80°C for 20 hrs the inorganic salts were removed by filtration, the filtrate was evaporated and the residue was treated with water and a small volume of 10 % aqueous ammonium hydroxide. The product was extracted with chloroform, and the organic layer was washed with aqueous sodium chloride and then dried (Na_2SO_4). After evaporation of the solvent the product was crystallized. For the preparation of 7e N-demethylthebaine (7a) was acylated with cyclobutanecarbonyl chloride in dichloromethane and in the presence of triethylamine (according to the Bentley method[14]), and the resulting amide was reduced with $LiAlH_4$ in tetrahydrofuran.

The preparation of 3b, 4d and 3d was accomplished as described by Currie et al[6].

N-Demethyl-N-substituted-14-hydroxycodeinone derivatives (8b, d)

A solution of N-demethyl-N-alkylthebaine (10 mmol) in 85 % formic acid (15 ml) was treated with 1.3 ml of 30 % hydrogen peroxide by stirring at 40°C for 6 hrs. After cooling, the reaction mixture was poured onto ice and the pH was adjusted to ~9-10 by the addition of ac. ammonium hydroxide. The crystalline products were isolated by filtration, or in the lack of crystalline precipitate, the mixture was extracted with chloroform. Pure products can be obtained by recrystallization or by means of column chromatography.

Reduction of 8a, 8b and 8d

To a cooled (5°C) solution of the 14-hydroxycodeinone derivative (1.0 g) in methanol (30 ml) sodium borohydride (1.0 g) was added in small portions and the mixture was stirred at room temperature for 2 hrs. The solvent was then removed under diminished pressure, the residue was treated with water (50 ml) and 5 % aqueous sodium hydroxide (5 ml), and extracted with chloroform. The crude products were purified by means of column chromatography to obtain compounds 2c, 2g and 2h. A similar

procedure was applied for the preparation of 14-trimethylsilyloxycodeine (6a → 6b).

N-Demethylation with vinyl chloroformate

To a solution of 3a or 3b (10 mmol) in dry 1,2-dichloroethane sodium hydrogen carbonate (2.5 g) and vinyl chloroformate (3.6 ml; 40 mmol) were added and the mixture was stirred under reflux for 8 hrs. When TLC examination showed an incomplete conversion, a further 3.6 ml portion of vinyl chloroformate was introduced, and stirring and reflux were continued for additional 8 hrs. After the removal of the inorganic salts by filtration, the filtrate was concentrated, the residue was dissolved in chloroform (100 ml) and washed with 1 % aqueous hydrochloric acid and water. The dried (Na_2SO_4) organic layer was concentrated under diminished pressure; when the starting material was 3a the vinylurethane derivative 3c was crystallized from methanol. The vinyluretane derivatives were then subjected to further transformation, without isolation, as follows. Dry hydrochloric acid gas was passed through a solution of the vinylurethanes in dry dichloromethane (50 ml) under stirring and external ice-cooling for 1 h. The solvent was then removed under diminished pressure, and the residue was boiled with abs. methanol (80 ml) for 3 hrs. After evaporation of the solvent in vacuo the hydrochloride salt was dissolved in water; in the case

of 3c addition of saturated aqueous sodium hydrogen carbonate induced O → N acetyl-migration (3c → 5).

For the preparation of 2e the aqueous solution was made alkaline (pH=9) by the addition of cc. ammonium hydroxide, and the product was isolated by extraction with chloroform, yield: 73 %.

For obtaining compounds 1b, 1c and 1d the method described by Rice[15] was employed.

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