

**SYNTHESIS OF *N*-DEMETHYL-*N*-SUBSTITUTED
14 β -HYDROXY-ISOMORPHINE AND DIHYDROISOMORPHINE
DERIVATIVES[#]**

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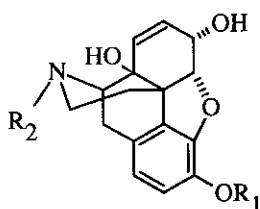
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Abstracts -- Some new representatives (3e-3h, 5g) of a new group of structurally related morphine-agonist and antagonist compounds have been prepared in stereochemically homogeneous forms. Application of the Mitsunobu-reaction for suitable codeine derivatives (1a-1d) gave the benzoates (2a-2d) of the hitherto unknown C-6 iso-compounds, which were converted into the desired isocodeines (3b-3d) by means of alkaline hydrolysis. *O*-Demethylation of these derivatives afforded the corresponding morphine analogues. The preparation of 3e was also carried out from 1f via compound (2e). A hitherto unknown *N*-demethylation also allowed the conversion of 3a and 5a into the target compounds. With the exception of *N*-allyl derivatives, the dihydro analogues were obtained by the hydrogenation of the C₇-C₈ double bond.

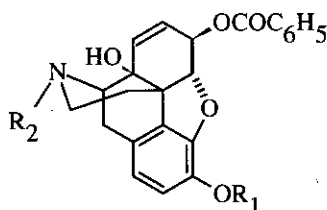
For structure-activity relationship studies, and most particularly, to investigate the agonist-antagonist effects with respect to the steric position of the C-6-OH group in certain stereochemically homogeneous representatives of structurally related morphine alkaloids, the synthesis of a series of new *N*-demethyl-*N*-alkyl-isomorphine,¹ dihydroisomorphine,² 14 β -hydroxymorphine³ and 14 β -hydroxydihydromorphine⁴ derivatives has been published recently.

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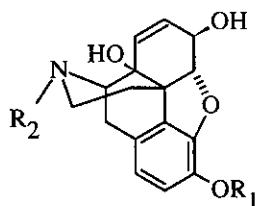
The present paper describes the preparation of novel *N*-demethyl-*N*-alkylisomorphine(isocodeine) and dihydroisomorphine(dihydroisocodeine) analogues, carrying a C-14 β -hydroxyl substituent. Among such compounds a few dihydro derivatives have already been synthesized, i.e. β -naltrexol⁵ (the human metabolite of naltrexone), 3-*O*-methyl- β -naltrexol,^{5a} β -naloxol,⁵ and β -oxymorphol⁵ (which latter was obtained from the corresponding ketone by reduction⁵ with formamidinesulfonic acid). In addition, the preparation of 14 β -hydroxyisocodeine⁶ and 14 β -hydroxydihydroisocodeine⁶ has also been published.



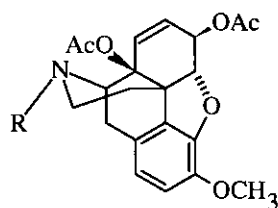
- 1a: R₁=CH₃; R₂=CH₃
 1b: R₁=CH₃; R₂=allyl
 1c: R₁=CH₃; R₂=C₃H₇
 1d: R₁=CH₃; R₂=CPM
 1e: R₁=H; R₂=CH₃
 1f: R₁=Ac; R₂=CH₃



- 2a: R₁=CH₃; R₂=CH₃
 2b: R₁=CH₃; R₂=allyl
 2c: R₁=CH₃; R₂=C₃H₇
 2d: R₁=CH₃; R₂=CPM
 2e: R₁=Ac; R₂=CH₃

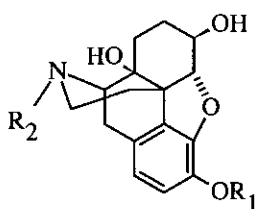


- 3a: R₁=CH₃; R₂=CH₃
 3b: R₁=CH₃; R₂=allyl
 3c: R₁=CH₃; R₂=C₃H₇
 3d: R₁=CH₃; R₂=CPM
 3e: R₁=H; R₂=CH₃
 3f: R₁=H; R₂=allyl
 3g: R₁=H; R₂=C₃H₇
 3h: R₁=H; R₂=CPM
 3i: R₁=CH₃; R₂=H

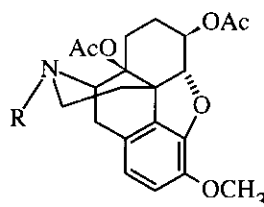


- 4a: R=CH₃
 4b: R=CO₂CH=CH₂
 4c: R=CN

The Mitsunobu-reaction,⁷ employed successfully for the synthesis¹ of *N*-demethyl-*N*-alkylisocodeines and isomorphines, was found to be suitable for the epimerization of the C-6 α hydroxyl group in the presence of a C-14 β -OH substituent. Thus, the reaction of the 14 β -hydroxycodine derivatives (1a-d) in benzene with benzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate readily afforded the epimeric benzoates (2a-d) in good yield (comparing of the yields of 14 β -H and 14 β -OH benzoates there were not significant differences), whose alkaline hydrolysis gave the desired 14 β -hydroxyisocodeines (3a-d). The stereochemistry of 6 β benzoates was established by the ¹H-nmr spectra with particular reference to the $J_{5,6}$ values ($J_{5,6}$ = 0.0-1.0 Hz¹⁵). For the synthesis of 14 β -hydroxyisomorphine (3e), the phenolic hydroxyl group of 14 β -hydroxymorphine (1e) was acetylated according to the Welsh procedure⁹ (to avoid the formation of alkyl phenyl ethers¹¹) and the resulting 1f was treated with benzoic acid under the conditions of the Mitsunobu-reaction (TPP, DEAD) to obtain 2e. Alkaline hydrolysis of the latter compound then furnished 3e.



- 5a: R₁=CH₃; R₂=CH₃
 5b: R₁=CH₃; R₂=allyl
 5c: R₁=CH₃; R₂=C₃H₇
 5d: R₁=CH₃; R₂=CPM
 5e: R₁=H; R₂=CH₃
 5f: R₁=H; R₂=allyl
 5g: R₁=H; R₂=C₃H₇
 5h: R₁=H; R₂=CPM
 5i: R₁=CH₃; R₂=H



- 6a: R=CH₃
 6b: R=CO₂CH=CH₂
 6c: R=CN

The *N*-demethyl-*N*-alkyl-14 β -hydroxyisomorphine derivatives (3f-h) were prepared by the *O*-demethylation (BBr₃, CHCl₃) of the corresponding isocodeines (3b-d). With the exception of 3b and 3f the C₇-C₈ double bond of the *N*-demethyl-*N*-alkyl derivatives was saturated by means of catalytic hydrogenation over Pd/C to obtain the corresponding dihydro compounds (5a, 5c-e, 5g,h).

Since *N*-demethylation of 3a and 5a has not been reported as yet, a novel and essentially different method was elaborated to achieve this conversion and to prepare the target compounds. Acetylation of 14 β -hydroxyisocodeine (3a) furnished the diacetate (4a), which was transformed into the urethane (4b) upon treatment with vinyl chloroformate.¹¹⁻¹³ However, splitting of 4b did not give a homogeneous product (similarly to that observed³ in the case of 14 β -hydroxycodine). The target compound (3i) could only be prepared by the LiAlH₄-reduction of the cyanamide (4c) (derived from 4a with cyanogen bromide), and then subsequent *N*-alkylation with *n*-propyl bromide gave rise to 3c, which was identical with the product of the Mitsunobu-reaction sequence (1c $\rightarrow$ 2c $\rightarrow$ 3c).

N-Demethylation of the diacetate⁶ (6a) of 14 β -hydroxydihydroisocodeine (5a) was accomplished both with cyanogen bromide and vinyl chloroformate, and cleavage of the produced cyanamide (6c) and urethane (6b), respectively, in the usual manner led to 5i. *N*-Alkylation of 5i gave the *N*-substituted derivatives (5b-d), from which the corresponding 14 β -hydroxydihydroisomorphine analogues (5f-h) can be obtained *O*-demethylation (with boron tribromide in chloroform).

EXPERIMENTAL

Melting points were determined with an "Electrothermal" digital instrument (Type 8103) in open capillary tubes and the data are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60F₂₅₄ foils using 8:2 benzene:methanol, 9:1 chloroform:methanol, and 5:4:1 chloroform:acetone:diethylamine developing systems. The spots were visualized by Dragendorff-reagent. For column chromatography Kieselgel 60 H absorbent and 9:1 benzene-methanol eluent were applied. ¹H-Nmr spectra were recorded with a Varian-Gemini 200 instrument and mass spectra were obtained with a VG-TRIO-2 spectrometer.

Table 1

Physical constants and elemental analytical data of the prepared compounds

Compound	Yield %	Cryst. solvent	mp °C	Formula	Analytical data			
					calculated		found	
					C%	N%	C%	N%
2a	62	EtOH	141-43	C ₂₅ H ₂₅ NO ₅	71.6	3.3	71.9	3.4
2b	72	--	syrup	C ₂₇ H ₂₇ NO ₅	---	---	---	---
2c	55	EtOH	142-45	C ₂₇ H ₂₉ NO ₅	72.5	3.1	72.4	3.3
2d	70	EtOH	137-38	C ₂₈ H ₂₉ NO ₅	73.2	3.0	72.8	3.1
2e	55	EtOH	196-98	C ₂₆ H ₂₅ NO ₆	69.8	3.1	69.6	3.2
3a*	81	EtOH	152-54	C ₁₈ H ₂₁ NO ₄	68.6	4.4	68.8	4.2
3b	62	--	syrup	C ₂₀ H ₂₃ NO ₄	---	---	---	---
3c	86	EtOH	125-26	C ₂₀ H ₂₅ NO ₄	69.9	4.1	69.7	4.0
3d	75	EtOH	99-100	C ₂₁ H ₂₅ NO ₄	71.0	3.9	71.3	3.8
3e	42	EtOH	246-50	C ₁₇ H ₁₉ NO ₄	67.8	4.6	67.9	4.5
3f	48	EtOH	214-17(HCl)	C ₁₉ H ₂₁ NO ₄ ·xHCl	62.7	3.9	62.9	3.8
3g	60	EtOH	163-64	C ₁₉ H ₂₃ NO ₄	69.3	4.3	69.0	4.2
3h	49	Et ₂ O	170-74	C ₂₀ H ₂₃ NO ₄	70.4	4.1	70.1	4.3
3i	22	EtOH	290(HCl)	C ₁₇ H ₁₉ NO ₄ ·xHCl	60.5	4.2	60.7	4.0
4b	61	MeOH	163-65	C ₂₅ H ₂₅ NO ₄	65.9	3.1	65.7	3.3
4c	57	EtOH	191-93	C ₂₂ H ₂₂ N ₂ O ₆	64.4	6.8	64.8	6.5
5b	53	benzene-petr. ether	112-13	C ₂₀ H ₂₅ NO ₄	69.9	4.1	70.2	4.3
5c	55	EtOAc	146-48	C ₂₀ H ₂₇ NO ₄	69.5	4.1	69.3	3.9
5d*	57	EtOH	173-75	C ₂₁ H ₂₇ NO ₄	71.0	3.9	71.3	3.7
5e*	75	EtOH	244-46	C ₁₇ H ₂₁ NO ₄	67.3	4.6	67.6	4.4
5f*	65	EtOH-Et ₂ O	203(HCl)	C ₁₉ H ₂₃ NO ₄ ·xHCl	62.4	3.8	62.2	4.0
5g	65	EtOH	263-65(HCl)	C ₁₉ H ₂₅ NO ₄ ·xHCl	62.0	3.8	61.8	3.7
5h*	81	EtOH	207(HCl)	C ₂₀ H ₂₅ NO ₄ ·xHCl	63.6	3.7	63.9	3.5
5i	90(6b→5i) 41(6c→5i)	EtOH	262(HCl)	C ₁₇ H ₂₁ NO ₄ ·xHCl	60.1	4.1	59.8	4.3
6b	82	MeOH	144-46	C ₂₄ H ₂₇ NO ₈	63.0	3.1	63.4	2.9
6c	56	EtOH	173-74	C ₂₂ H ₂₄ N ₂ O ₆	64.1	6.8	64.3	6.5

* 3a: 149-150⁶; 5d: 172-173^{5a}; 5e: 248-250¹⁴; 5f: 205-207⁵; 5h: 205-208⁵

Table 2.

Representative ^1H -nmr and ms data for compounds (**2-6**)^{##}

Compd	δ (ppm) CDCl_3 (* $\text{DMSO}-d_6$, # D_2O)	Ms (%)
2a	2.4(s, 3H, NMe); 3.9(s, 3H, OMe); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.5(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.9(d, 1H, C_8H); 6.2(m, 1H, C_7H); 6.7(ABq, 2H, ArH); 7.2-8.2(m, 5H, $\text{C}_6\text{H}_5\text{CO}_2$)	419[M ⁺]
2b	3.9(s, 3H, OMe); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.2-5.3(m, 2H, allyl CH_2); 5.5(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.8-6.0(m, 2H, C_8H and allyl CH); 6.2(m, 1H, C_7H); 6.7(ABq, 2H, ArH); 7.2-8.2(m, 5H, $\text{C}_6\text{H}_5\text{CO}_2$)	445[M ⁺] 341(20) 324(30)
2c	0.9-1.0(t, 3H, propyl Me); 3.9(s, 3H, OMe); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.5(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.9(dd, 1H, C_8H); 6.2(m, 1H, C_7H); 6.7(ABq, 2H, ArH); 7.2-8.1(m, 5H, $\text{C}_6\text{H}_5\text{CO}_2$)	447[M ⁺] 418(45) 326(75)
2d	0.1-0.2(m, 5H, cyclopropyl H); 3.9(s, 3H, OMe); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.5(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.9(d, 1H, C_8H); 6.2(m, 1H, C_7H); 6.7(ABq, 2H, ArH)	459[M ⁺]
2e	2.3(s, 3H, C_3OAc); 2.4(s, 3H, NMe); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.5(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.9(d, 1H, C_8H); 6.2(m, 1H, C_7H); 6.7(ABq, 2H, ArH); 7.2-8.2(m, 5H, $\text{C}_6\text{H}_5\text{CO}_2$)	447[M ⁺] 325(42) 283(42)
3a	2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.1(d, 1H, $\text{C}_{6\alpha}\text{H}$); 4.8(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.8(d, 1H, C_8H); 6.3(m, 1H, C_7H); 6.7(ABq, 2H, ArH)	315[M ⁺]
3b	3.8(s, 3H, OMe); 4.1(dd, 1H, $\text{C}_{6\alpha}\text{H}$); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.1-5.3(m, 3H, allyl CH_2 and C_{14}OH); 5.7-5.9(m, 2H, C_8H and allyl CH); 6.4(m, 1H, C_7H); 6.7(ABq, 2H, ArH)	341[M ⁺]
3c	0.9-1.0(t, 3H, propyl Me); 3.8(s, 3H, OMe); 4.1(d, 1H, $\text{C}_{6\alpha}\text{H}$); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.8(d, 1H, C_8H); 6.4(m, 1H, C_7H); 6.7(ABq, 2H, ArH)	343[M ⁺] 314(100)
3d	0.1-0.2(m, 5H, cyclopropyl H); 3.9(s, 3H, OMe); 4.2(d, 1H, $\text{C}_{6\alpha}\text{H}$); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.8(d, 1H, C_8H); 6.4(m, 1H, C_7H); 6.7(ABq, 2H, ArH)	355[M ⁺]
3e*	2.3(s, 3H, NMe); 4.5(s, 1H, $\text{C}_{5\beta}\text{H}$); 4.8(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.7(d, 1H, C_8H); 5.9(m, 1H, C_7H); 6.7(ABq, 2H, ArH)	301[M ⁺]
3f	4.1(s, 1H, $\text{C}_{6\alpha}\text{H}$); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.1-5.3(m, 2H, allyl CH_2); 5.7-5.9(m, 2H, C_8H and allyl CH); 6.3(m, 1H, C_7H); 6.5-6.7(ABq, 2H, ArH)	327[M ⁺]
3g	0.9-1.0(t, 3H, propyl Me); 4.1(m, 1H, $\text{C}_{6\alpha}\text{H}$); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.8(d, 1H, C_8H); 6.4(m, 1H, C_7H); 6.5-6.7(ABq, 2H, ArH)	331[M ⁺] 302(100)
3h	0.1-0.9(m, 5H, cyclopropyl H); 4.2(d, 1H, $\text{C}_{6\alpha}\text{H}$); 4.9(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.8(d, 1H, C_8H); 6.3(m, 1H, C_7H); 6.5-6.7(ABq, 2H, ArH)	341[M ⁺]

Table 2 continued

Compd	δ (ppm) CDCl_3 (* $\text{DMSO}-d_6$, # D_2O)	Ms (%)
3i [#]	4.1(s, 3H, OMe); 5.2(s, 1H, $\text{C}_{5\beta}\text{H}$); 6.2-6.3(d, 1H, C_8H); 6.4(m, 1H, C_7H); 7.1-7.2(ABq, 2H, ArH)	301[M ⁺]
4b	2.0-2.1(s, 6H, C_6OAc and C_{14}OAc); 3.9(s, 3H, OMe); 4.5(m, 1H, C_9H); 4.7-4.9(m, 2H, $\text{C}_{5\beta}\text{H}$ and vinyl H); 5.3(m, 1H, $\text{C}_{6\alpha}\text{H}$); 5.5(m, 1H, vinyl H); 6.0-6.1(m, 1H, C_7H); 6.4(m, 1H, C_8H); 6.6-6.8(ABq, 2H, ArH); 7.2(m, 1H, vinyl H)	455[M ⁺]
4c	2.1(s, 3H, C_6OAc); 2.2(s, 3H, C_{14}OAc); 3.9(s, 3H, OMe); 4.6(d, 1H, C_9H); 4.8(s, 1H, $\text{C}_{5\beta}\text{H}$); 5.3(m, 1H, $\text{C}_{6\alpha}\text{H}$); 5.5(m, 1H, vinyl H); 6.1(m, 1H, C_7H); 6.3(m, 1H, C_8H); 6.6-6.8(ABq, 2H, ArH)	410[M ⁺]
5b	3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 3.9(s, 3H, OMe); 4.5(d, 1H, $\text{C}_{5\beta}\text{H}$); 5.1-5.3(m, 2H, allyl CH_2); 5.7-5.9(m, 1H, allyl CH); 6.6-6.8(ABq, 2H, ArH)	343[M ⁺]
5c	0.9(t, 3H, propyl Me); 3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 3.9(s, 3H, OMe); 4.5(d, 1H, $\text{C}_{5\beta}\text{H}$); 6.6-6.8(ABq, 2H, ArH)	345[M ⁺] 316(100)
5d	0.1-0.9(m, 5H, cyclopropyl H); 3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 3.9(s, 1H, OMe); 4.5(d, 1H, $\text{C}_{5\beta}\text{H}$); 6.6-6.8(ABq, 2H, ArH)	357[M ⁺]
5e [*]	2.4(s, 3H, NMe); 4.2(d, 1H, $\text{C}_{6\alpha}\text{H}$); 5.0(d, 1H, $\text{C}_{5\beta}\text{H}$); 6.5(ABq, 2H, ArH)	303[M ⁺]
5f	3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 4.6(d, 1H, $\text{C}_{5\beta}\text{H}$); 5.1-5.3(m, 2H, allyl CH_2); 5.7-5.9(m, 1H, allyl CH); 6.5-6.7(ABq, 2H, ArH)	329[M ⁺]
5g	0.9(t, 3H, propyl Me); 3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 4.5(d, 1H, $\text{C}_{5\beta}\text{H}$); 6.6-6.8(ABq, 2H, ArH)	331[M ⁺]
5h	0.1-0.9(m, 5H, cyclopropyl H); 3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 4.6(d, 1H, $\text{C}_{5\beta}\text{H}$); 6.5-6.7(ABq, 2H, ArH)	343[M ⁺]
5i	3.6(m, 1H, $\text{C}_{6\alpha}\text{H}$); 3.9(s, 3H, OMe); 4.5(d, 1H, $\text{C}_{5\beta}\text{H}$); 6.6-6.8(ABq, 2H, ArH)	
6b	2.0-2.1(2s, 6H, C_6OAc and C_{14}OAc); 3.9(s, 3H, OMe); 4.4-4.9(m, 4H, $\text{C}_{5\beta}\text{H}$, $\text{C}_{6\alpha}\text{H}$, C_9H and vinyl CH); 5.5-5.6(m, 1H, vinyl CH); 6.6-6.8(ABq, 2H, ArH); 7.1-7.2(m, 1H, vinyl CH)	457[M ⁺]
6c	2.1(s, 3H, C_6OAc); 2.3(s, 3H, C_{14}OAc); 3.9(s, 3H, OMe); 4.6-4.8(m, 3H, $\text{C}_{5\beta}\text{H}$, $\text{C}_{6\alpha}\text{H}$ and C_9H); 6.7-6.8(ABq, 2H, ArH)	412[M ⁺]

Table 3. ^1H , ^1H coupling constant (Hz)

Compound	$J(\text{H},\text{H})$ (Hz)					
	1,2	5,6	5,7	6,7		7,8
2a	8.2	~1	~1	5.4		10.0
2b	8.1	~1	~1	5.5		10.0
2c	8.2	~1	~1	5.3		10.1
2d	8.2	~1	~1	5.4		9.9
2e	8.2	~1	~1	5.4		9.8
3a	8.1	~1	~1	6.0		9.5
3b	8.2	~1	~1	6.1		9.6
3c	8.2	~1	~1	6.1		9.5
3d	8.2	~1	~1	6.2		9.7
3e	8.2	~1	~1	5.5		9.8
3f	8.1	~1	~1	6.2		9.7
3g	8.2	~1	~1	6.3		9.8
3h	8.2	~1	~1	6.5		9.2
3i*	8.1	~1	~1	4.8		10.0
4b	8.2	~1	~1	6.2		9.8
4c	8.2	~1	~1	5.9		9.9
5b	8.2	5.5	0	10.1(a)	4.8(e)	nd
5c	8.2	5.5	0	10.0(a)	4.7(e)	nd
5d	8.3	5.5	0	10.0(a)	4.7(e)	nd
5g	8.4	5.9	0	10.2(a)	4.5(e)	nd
5i	8.2	5.5	0	nd	nd	nd
6b	8.2	nd	nd	nd	nd	nd
6c	8.2	5.0	1.8	11.0(a)	5.8(e)	nd

* HCl salt in $\text{DMSO}-d_6$ as solvent

nd : not determined because of strong coupling

GENERAL PROCEDURES

Preparation of Compounds 2 (Mitsunobu-esterification procedure)

Compound (1a-d or 1f) (10 mmol), triphenylphosphine (5.24 g, 20mmol) and benzoic acid (2.44 g, 20 mmol) were dissolved in anhydrous benzene (100 ml) and diethyl azodicarboxylate (3.4 ml, 20 mmol) dissolved in anhydrous benzene(10 ml) was dropwise added over a period of 5-10 min. The reaction mixture was stirred for another 1 h and the precipitate was filtered off. The solvent was evaporated, the syrupy residue treated with D-tartaric acid (2.0-2.5 g) dissolved in 100 ml of water and extracted with ether. The aqueous phase was alkaliized with 10% ammonium hydroxide and extracted with chloroform. The chloroform solution was washed with brine, then with water, dried over sodium sulfate, the solvent was evaporated, and the residue was crystallized from ethanol.

General Procedure for the Hydrolysis of Benzoic Acid Esters

A mixture of compound (2) (1.0 g), 10% aqueous KOH solution (10ml), and ethanol (10ml) was refluxed for 10 min, then the pH of the mixture was adjusted to 8-9 with 10% ammonium hydroxide and extracted with chloroform. The organic phase was washed with brine, then with water, dried over sodium sulfate, the solvent was evaporated and the residue was crystallized to afford compounds (3).

N-Demethylation with Vinyl Chloroformate

To a solution of (4a or 6a) (10mmol) in dry 1,2-dichloroethane (80 ml) sodium hydrogen carbonate (2.5 g 31.3 mmol) and vinyl chloroformate (3.6 ml, 40mmol) were added and the mixture was stirred under reflux for 8 h. When tlc examination showed an incomplete conversion, a further 3.6 ml (40 mmol) portion of vinyl chloroformate was introduced, and stirring and reflux was continued for additional 8 h. After the removal of the inorganic salts by filtration the filtrate was concentrated, the residue was dissolved in chloroform (100ml) and washed with 1% hydrochloric acid and water. The dried (Na_2SO_4) organic layer was concentrated under diminished pressure; the vinylurethane derivatives (4b and 6b) were crystallized from methanol. The vinylurethane derivative (6b) was then subjected to further transformation, without isolation, as follows. Dry hydrochloric acid gas was passed through a solution of the vinylurethane 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 h. After evaporation of the solvent *in vacuo* the hydrochloride salt was dissolved in 10% hydrochloric acid and was heated at 100 °C for 4 h. For the preparation of 5i the aqueous solution was made alkaline (pH=9) by the addition of conc. ammonium hydroxide, and the product was isolated by extraction with chloroform. 5i was characterized as its hydrochloride salt.

N-Demethylation with Cyanogen Bromide

To a solution of the *N*-methyl compound (**4a** or **6a**) (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 the 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% hydrochloric acid and water and then dried (Na₂SO₄). After evaporation the residual solid crude cyanamides (**4c** and **6c**) were crystallized from ethanol. In the case of **6c** the cyanamide was suspended in a tenfold excess of 10% 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. For the preparation of **3i** the reduction of **4c** with LiAlH₄ was successfully applied.

N-Alkylation Methods (alkylation of **3i** and **5i**)

To a solution of **3i** or **5i** (10 mmol) in dry *N,N*-dimethylformamide (15 ml) powdered sodium hydrogen carbonate (1.2 g, 14.3 mmol) and the appropriate alkyl bromide (12 mmol) were added. After stirring at 80 °C for 20 h the inorganic salts were removed by filtration, the filtrate was evaporated and the residue was treated with water and a small volume of 10 % ammonium hydroxide. The product was extracted with chloroform, and the organic layer was washed with aqueous sodium chloride and then dried (Na₂SO₄). After evaporation of the solvent the product was crystallized.

O-Demethylation with Boron Tribromide

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 ammonium hydroxide. The chloroform layer was separated and the aqueous phase was extracted with chloroform (3x20 ml). The combined organic extract were washed with aq. sodium chloride, dried and concentrated

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