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

**Sándor Hosztafi[1], Csaba Simon[1], and Sándor Makleit*[2]**

**[1]Alkaloida Chemical Company Ltd., H-4440, Tiszavasvári, Hungary**

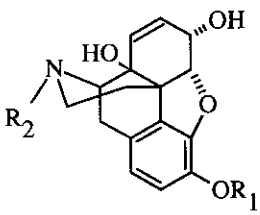
**[2]Department of Organic Chemistry, L. Kossuth University, H-4010 Debrecen, Hungary**

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 $C_7$-$C_8$ double bond.

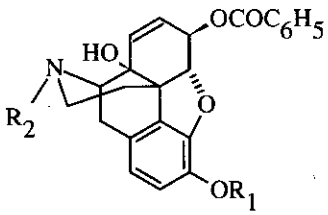
For structure-activity relationship studies, and most particularly, to investigate the agonist-antagonist effects with respect to the steric position of the C-6-OH group in certain stereochemically homogeneous representatives of structurally related morphine alkaloids, the synthesis of a series of new *N*-demethyl-*N*-alkyl-isomorphine,[1] dihydroisomorphine,[2] 14β-hydroxymorphine[3] and 14β-hydroxydihydromorphine[4] derivatives has been published recently.

* Author to whom correspondence should be adressed

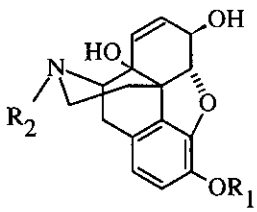
The present paper describes the preparation of novel *N*-demethyl-*N*-alkylisomorphine(isocodeine) and dihydroisomorphine(dihydroisocodeine) analogues, carrying a C-14β-hydroxyl substituent. Among such compounds a few dihydro derivatives have already been synthesized, i.e. β-naltrexol[5] (the human metabolite of naltrexone), 3-*O*-methyl-β-naltrexol,[5a] β-naloxol,[5] and β-oxymorphol[5] (which latter was obtained from the corresponding ketone by reduction[5] with formamidinesulfinic acid). In addition, the preparation of 14β-hydroxyisocodeine[6] and 14β-hydroxydihydroisocodeine[6] has also been published.



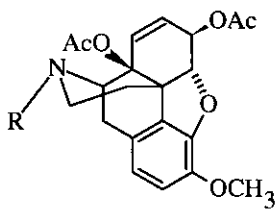
1a: $R_1$=$CH_3$; $R_2$=$CH_3$
1b: $R_1$=$CH_3$; $R_2$=allyl
1c: $R_1$=$CH_3$; $R_2$=$C_3H_7$
1d: $R_1$=$CH_3$; $R_2$=CPM
1e: $R_1$=H; $R_2$=$CH_3$
1f: $R_1$=Ac; $R_2$=$CH_3$



2a: $R_1$=$CH_3$; $R_2$=$CH_3$
2b: $R_1$=$CH_3$; $R_2$=allyl
2c: $R_1$=$CH_3$; $R_2$=$C_3H_7$
2d: $R_1$=$CH_3$; $R_2$=CPM
2e: $R_1$=Ac; $R_2$=$CH_3$

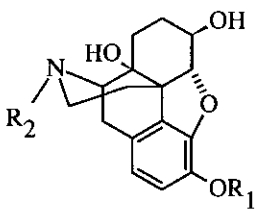


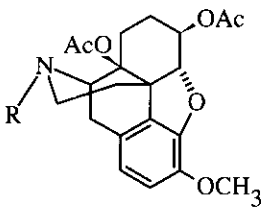
3a: $R_1$=$CH_3$; $R_2$=$CH_3$
3b: $R_1$=$CH_3$; $R_2$=allyl
3c: $R_1$=$CH_3$; $R_2$=$C_3H_7$
3d: $R_1$=$CH_3$; $R_2$=CPM
3e: $R_1$=H; $R_2$=$CH_3$
3f: $R_1$=H; $R_2$=allyl
3g: $R_1$=H; $R_2$=$C_3H_7$
3h: $R_1$=H; $R_2$=CPM
3i: $R_1$=$CH_3$; $R_2$=H



4a: R=$CH_3$
4b: R=$CO_2CH{=}CH_2$
4c: R=CN

The Mitsunobu-reaction,[7] employed succesfully for the synthesis[1] of *N*-demethyl-*N*-alkylisocodeines and isomorphines, was found to be suitable for the epimerization of the C-6α hydroxyl group in the presence of a C-14β-OH substituent. Thus, the reaction of the 14β-hydroxycodeine 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 14β-H and 14β-OH benzoates there were not significant differences), whose alkaline hydrolysis gave the desired 14β-hydroxyisocodeines (3a-d). The stereochemistry of 6β benzoates was established by the $^1$H-nmr spectra with particular reference to the $J_{5,6}$values ($J_{5,6}$= 0.0-1.0 Hz[15]). For the synthesis of 14β-hydroxyisomorphine (3e), the phenolic hydroxyl group of 14β-hydroxymorphine (1e) was acetylated according to the Welsh procedure[9] (to avoid the formation of alkyl phenyl ethers[11]) 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: $R_1$=$CH_3$; $R_2$=$CH_3$
5b: $R_1$=$CH_3$; $R_2$=allyl
5c: $R_1$=$CH_3$; $R_2$=$C_3H_7$
5d: $R_1$=$CH_3$; $R_2$=CPM
5e: $R_1$=H; $R_2$=$CH_3$
5f: $R_1$=H; $R_2$=allyl
5g: $R_1$=H; $R_2$=$C_3H_7$
5h: $R_1$=H; $R_2$=CPM
5i: $R_1$=$CH_3$; $R_2$=H

6a: R=$CH_3$
6b: R=$CO_2CH$=$CH_2$
6c: R=CN

The *N*-demethyl-*N*-alkyl-14β-hydroxyisomorphine derivatives (3f-h) were prepared by the *O*-demethylation ($BBr_3$, $CHCl_3$) of the corresponding isocodeines (3b-d). With the exception of 3b and 3f the $C_7$-$C_8$ double bond of the *N*-demethyl-*N*-alkyl derivatives was saturared 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 14β-hydroxy-isocodeine (3a) furnished the diacetate (4a), which was tansformed into the urethane (4b) upon treatment with vinyl chloroformate.[11-13] However, splitting of 4b did not give a homogeneous product (similarly to that observed[3] in the case of 14β-hydroxycodeine ). The target compound (3i) could only be prepared by the $LiAlH_4$-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→ 2c→3c).

*N*-Demethylation of the diacetate[6] (6a) of 14β-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 14β-hydroxydihydroisomorphine anlogues (5f-h) can be obtained *O*-demethylation (with boron tribromide in chloroform).

## EXPERIMENTAL

Melting points were determined with an "Electrotermal" digital instrument (Type 8103) in open capillary tubes and the data are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 $F_{254}$ 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. $^1$H-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 datan of the prepared compounds

| Compound | Yield % | Cryst. solvent | mp °C | Formula | Analytical data calculated C% | N% | found 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) | $C_{19}H_{21}NO_4xHCl$ | 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 | Et2O | 170-74 | $C_{20}H_{23}NO_4$ | 70.4 | 4.1 | 70.1 | 4.3 |
| **3i** | 22 | EtOH | 290(HCl) | $C_{17}H_{19}NO_4xHCl$ | 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 | $C_{22}H_{22}N_2O_6$ | 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-$Et_2O$ | 203(HCl) | $C_{19}H_{23}NO_4xHCl$ | 62.4 | 3.8 | 62.2 | 4.0 |
| **5g** | 65 | EtOH | 263-65(HCl) | $C_{19}H_{25}NO_4xHCl$ | 62.0 | 3.8 | 61.8 | 3.7 |
| **5h*** | 81 | EtOH | 207(HCl) | $C_{20}H_{25}NO_4xHCl$ | 63.6 | 3.7 | 63.9 | 3.5 |
| **5i** | 90(6b→5i) 41(6c→5i) | EtOH | 262(HCl) | $C_{17}H_{21}NO_4xHCl$ | 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 | $C_{22}H_{24}N_2O_6$ | 64.1 | 6.8 | 64.3 | 6.5 |

* **3a:** 149-150[6]; **5d:** 172-173[5a]; **5e:** 248-250[14]; **5f:** 205-207[5]; **5h:** 205-208[5]

Table 2.

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

| Compd | δ (ppm) $CDCl_3$ (* DMSO-$d_6$, # $D_2O$) | Ms (%) |
|---|---|---|
| **2a** | 2.4(s, 3H, NMe); 3.9(s, 3H, OMe); 4.9(s, 1H, $C_{5\beta}H$); 5.5(d, 1H, $C_{6\alpha}H$); 5.9(d, 1H, $C_8H$); 6.2(m, 1H, $C_7H$); 6.7(ABq, 2H, ArH); 7.2-8.2(m, 5H, $C_6H_5CO_2$) | 419[$M^+$] |
| **2b** | 3.9(s, 3H, OMe); 4.9(s, 1H, $C_{5\beta}H$); 5.2-5.3(m, 2H, allyl $CH_2$); 5.5(d, 1H, $C_{6\alpha}H$); 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, $C_6H_5CO_2$) | 445[$M^+$]<br>341(20)<br>324(30) |
| **2c** | 0.9-1.0(t, 3H, propyl Me); 3.9(s, 3H, OMe); 4.9(s, 1H, $C_{5\beta}H$); 5.5(d, 1H, $C_{6\alpha}H$); 5.9(dd, 1H, $C_8H$); 6.2(m, 1H, $C_7H$); 6.7(ABq, 2H, ArH); 7.2-8.1(m, 5H, $C_6H_5CO_2$) | 447[$M^+$]<br>418(45)<br>326(75) |
| **2d** | 0.1-0.2(m, 5H, cyclopropyl H); 3.9(s, 3H, OMe); 4.9(s, 1H, $C_{5\beta}H$); 5.5(d, 1H, $C_{6\alpha}H$); 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, $C_{5\beta}H$); 5.5(d, 1H, $C_{6\alpha}H$); 5.9(d, 1H, $C_8H$); 6.2(m, 1H, $C_7H$); 6.7(ABq, 2H, ArH); 7.2-8.2(m, 5H, $C_6H_5CO_2$) | 447[$M^+$]<br>325(42)<br>283(42) |
| **3a** | 2.4(s, 3H, NMe); 3.8(s, 3H, OMe); 4.1(d, 1H, $C_{6\alpha}H$); 4.8(s, 1H, $C_{5\beta}H$); 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, $C_{6\alpha}H$); 4.9(s, 1H, $C_{5\beta}H$); 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, $C_8H$); 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, $C_{6\alpha}H$); 4.9(s, 1H, $C_{5\beta}H$); 5.8(d, 1H, $C_8H$); 6.4(m, 1H, $C_7H$,); 6.7(ABq, 2H, ArH) | 343[$M^+$]<br>314(100) |
| **3d** | 0.1-0.2(m, 5H, cyclopropyl H); 3.9(s, 3H, OMe); 4.2(d, 1H, $C_{6\alpha}H$); 4.9(s, 1H, $C_{5\beta}H$); 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, $C_{5\beta}H$); 4.8(d, 1H, $C_{6\alpha}H$); 5.7(d, 1H, $C_8H$); 5.9(m, 1H, $C_7H$); 6.7(ABq, 2H, ArH) | 301[$M^+$] |
| **3f** | 4.1(s, 1H, $C_{6\alpha}H$); 4.9(s, 1H, $C_{5\beta}H$); 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, $C_{6\alpha}H$); 4.9(s, 1H, $C_{5\beta}H$); 5.8(d, 1H, $C_8H$); 6.4(m, 1H, $C_7H$); 6.5-6.7(ABq, 2H, ArH) | 331[$M^+$]<br>302(100) |
| **3h** | 0.1-0.9(m, 5H, cyclopropyl H); 4.2(d, 1H, $C_{6\alpha}H$); 4.9(s, 1H, $C_{5\beta}H$); 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) $CDCl_3$ (* DMSO-$d_6$, # $D_2O$) | Ms (%) |
|---|---|---|
| **3i**# | 4.1(s,3H,OMe); 5.2(s, 1H, $C_{5\beta}H$); 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, $C_{5\beta}H$ and vinyl H); 5.3(m, 1H, $C_{6\alpha}H$); 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, $C_{5\beta}H$); 5.3(m, 1H, $C_{6\alpha}H$); 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, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 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, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 6.6-6.8(ABq, 2H,ArH) | 345[$M^+$] 316(100) |
| **5d** | 0.1-0.9(m, 5H, cyclopropyl H); 3.6(m, 1H, $C_{6\alpha}H$); 3.9(s,1H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 6.6-6.8(ABq, 2H, ArH) | 357[$M^+$] |
| **5e*** | 2.4(s, 3H, NMe); 4.2(d, 1H, $C_{6\alpha}H$); 5.0(d, 1H, $C_{5\beta}H$); 6.5(ABq, 2H, ArH) | 303[$M^+$] |
| **5f** | 3.6(m, 1H, $C_{6\alpha}H$); 4.6(d, 1H, $C_{5\beta}H$); 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, $C_{6\alpha}H$); 4.5(d, 1H, $C_{5\beta}H$); 6.6-6.8(ABq, 2H, ArH) | 331[$M^+$] |
| **5h** | 0.1-0.9(m, 5H, cyclopropyl H); 3.6(m, 1H, $C_{6\alpha}H$); 4.6(d, 1H, $C_{5\beta}H$); 6.5-6.7(ABq, 2H, ArH) | 343[$M^+$] |
| **5i** | 3.6(m, 1H, $C_{6\alpha}H$); 3.9(s, 3H, OMe); 4.5(d, 1H, $C_{5\beta}H$); 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, $C_{5\beta}H$, $C_{6\alpha}H$, $C_9H$ 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, $C_{5\beta}H$, $C_{6\alpha}H$ and $C_9H$); 6.7-6.8(ABq, 2H, ArH) | 412[$M^+$] |

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

| Compound | J (H,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 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 alkalized 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 (40ml) a solution of cyanogen bromide (1.5g, 14 mmol) in chloroform (20 ml) was added and the mixture was refluxed at 60 °C for 8 h. Then a second volume (1.5g, 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 ($Na_2SO_4$). 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 $LiAlH_4$ was succesfully applied.

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

To a solution of 3i or 5i (10mmol) 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 ($Na_2SO_4$). 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, 12mmol) 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

This work was financially supported in part, by a grant (OTKA I/3 reg. No.: 1722) obtained from the Hungarian Academy of Sciences..

**REFERENCES:**

#Morphine Alkaloids Paper 120, for part of 119 of this series see:

S. Berényi, S. Hosztafi, and S. Makleit, J. Chem. Soc., Perkin Trans. 1, 1992, 2693.

1. Cs. Simon, S. Hosztafi, and S. Makleit, Synth. Commun., 1991, 21, 407.
2. S. Hosztafi, Cs. Simon, and S. Makleit, Synth. Commun., 1992, 22, 1673.
3. S. Hosztafi, Cs. Simon, and S. Makleit, Synth. Commun., 1992, 22, 2527.
4. S. Hosztafi, S. Berényi, G. Tóth, and S. Makleit, Monatsh. Chem., 1992, 123, 435.
5. N. Chatterjie, C.E. Inturrisi, H.B. Dayton, and H. Blumberg, J. Med. Chem., 1975, 18, 490.

5a. G.A. Brine, K.G. Boldt, M.L. Coleman, D.J. Bradley, and F.I. Carroll, J. Org. Chem., 1978, 43, 1555.

6. A.C. Currie, G.T. Newbold, and F.S. Spring, J. Chem. Soc. 1961, 4693.
7. O. Mitsunobu, Synthesis 1981, 1.
8. U. Weiss and S.J. Daum, J. Med. Chem., 1965, 8, 1965, 123.
9. L.A. Welsh, J. Org. Chem., 1954 19, 1409.
10. M.S. Manhas, W.H. Hoffman, B. Lal and A.K. Bose, J. Chem. Soc., Perkin Trans. 1., 1975, 461.
11. R.A. Olofson, R.C. Schnur, L. Bunes, and J.P. Pepe, Tetrahedron Lett., 1977, 1567.
12. R.A. Olofson and R.C. Schnur, Tetrahedron Lett., 1977, 1571.
13. R.A. Olofson and J.P. Pepe, Tetrahedron Lett., 1977, 1575.
14. N. Chatterjie, J.G. Umans, and C.E. Inturrisi, J. Org. Chem., 1976, 41, 3624.
15. L. Szilágyi, S.Makleit, S. Hosztafi, and Cs. Simon, Magn. Reson. Chem., 1992, 30, 552.

Received, 30th November, 1992